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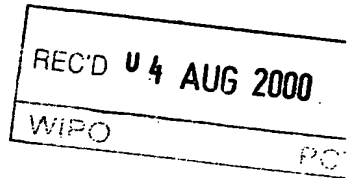
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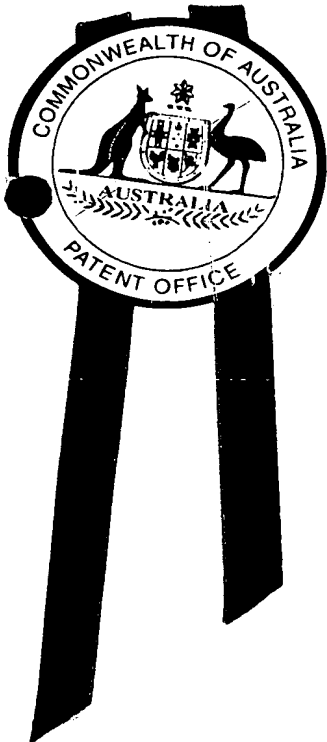


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I, KAY WARD, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ1675 for a patent by ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH filed on 19 July 1999.

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K Ward

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PROVISIONAL SPECIFICATION

Applicant(s):

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH

Invention Title:

INHIBITOR OF OSTEOCLAST PRECURSOR FORMATION

The invention is described in the following statement:

INHIBITOR OF OSTEOCLAST PRECURSOR FORMATION

This invention relates to a polypeptide factor which is able to inhibit the formation of osteoclasts. In particular, the invention relates to a factor which inhibits the differentiation of haematopoietic precursor cells into mononucleate osteoclast precursors. In a preferred form of the invention, the factor is a type II membrane polypeptide expressed on the osteoblast cell surface, which we have designated osteoclast inhibitory lectin (OCIL).

BACKGROUND OF THE INVENTION

In normal adults, the processes of bone formation and resorption are balanced in order to maintain a normal healthy bone mass. With the onset of the menopause in females and with ageing in both sexes, the rate of bone resorption exceeds that of bone formation, resulting in net bone loss, and ultimately in osteoporosis.

Osteoblasts are the bone cells responsible for bone formation, while osteoclasts are responsible for resorption of bone. Our understanding of the factors that regulate the formation and function of osteoclasts has been greatly enhanced by laboratory methods that have enabled us to isolate and grow these cells in culture. It is now well established that the development of active osteoclasts *in vitro* requires intimate contact between osteoblastic stromal cells and precursors of osteoclasts which are derived from haematopoietic cells belonging to the monocyte/macrophage lineage (Takahashi *et al*, 1988). This process is influenced by a variety of factors, including 1,25-dihydroxyvitamin D₃, parathyroid hormone, prostaglandin E₂, and interleukins 6, 11 and 17, all of which enhance osteoclast formation. In contrast, cytokines such as interleukins 4, 10, 13 and 18 are inhibitory (Suda *et al*, 1995; Martin and Udagawa, 1998).

All factors which stimulate osteoclast formation act directly on the osteoblast population and not on the osteoclast precursors, leading to the proposal that osteoblasts or stromal cells express a membrane-associated peptide that regulates the formation of functional multinucleate osteoclasts. A factor, termed "Osteoclast Differentiation Factor" (ODF), that fulfils the functions of such a putative membrane-associated peptide has recently been cloned. ODF encodes a 316 amino acid type II transmembrane protein, and is a member of the TNF ligand family (Yasuda et al, 1998). Recombinant protein corresponding to the extracellular domain of ODF stimulates the formation of active, bone-resorbing osteoclasts from haematopoietic cells within the spleen, even in the absence of stromal cells. A peptide identical to ODF has also been cloned from T cells, and designated Tumour Necrosis Factor-related activation-induced cytokine (TRANCE), or receptor activator of NF- κ B ligand (RANKL) (Wong et al, 1997). When released by T cells following activation of the T cell receptor, it mediates the interaction of T cells and dendritic cells, resulting in stimulation as well as increased survival of the naïve T cells. RANK, another member of the TNF-receptor family, has been identified on dendritic cells, and acts as the receptor for TRANCE/RANKL (Anderson et al, 1997).

Osteoprotegerin (OPG) is a soluble factor that belongs to the Tumour Necrosis Factor (TNF) receptor family. This factor is also known as Osteoclastogenesis Inhibitory Factor (OCIF). It has been shown to bind to ODF, resulting in the inhibition of formation of functional multinucleate osteoclasts *in vitro*. OPG is a 401 amino acid polypeptide. Overexpression of OPG in transgenic mice results in severe osteopetrosis, with a loss of bone marrow cavities and profound depletion of osteoclasts. The same effects were observed upon administration of OPG to normal mice. Furthermore, OPG blocked ovariectomy-associated bone loss in rat. OPG mRNA transcripts have been identified

within bone and cartilage, vascular structures, midgut and kidney, and in several osteoblast cell lines. Current data suggest that OPG blocks the terminal stages of osteoclast differentiation, but not the formation of mononuclear
5 osteoclast precursors (Simonet *et al*, 1997; Tsuda *et al*, 1997).

The interaction between ODF and OPG in the formation of osteoclasts is illustrated in Figure 1. Osteoclasts are derived from haematopoietic stem cells that
10 differentiate along the monocyte/macrophage lineage. Mononuclear precursors of osteoclasts are required to come into direct or close contact with osteoblasts to be rendered capable of differentiating into mature, functional, multinucleate osteoclasts. Osteoblasts express
15 ODF, a membrane-bound protein that stimulates the differentiation and formation of multinucleate osteoclasts from mononuclear precursors when it binds to its receptor, RANK. ODF expression is stimulated by bone-resorbing factors such as PTH, PGE₂, 1,25-dihydroxyvitamin D₃ and
20 interleukins 6 and 11. The action of ODF is antagonised by Osteoprotegerin, a soluble factor secreted by osteoblastic stromal cells. It binds to ODF to inhibit the formation of differentiated multinucleate osteoclasts, but does not prevent the formation of mononuclear osteoclast precursors.

25 We have now identified a polypeptide factor which is able to inhibit formation of mononuclear osteoclast precursors from haematopoietic stem cells, and which is expressed at least on the cell membranes of osteoblasts. It appears that when the molecule is expressed on the
30 osteoblast cell membrane it is not secreted. Preventing expression of the factor results in increased formation of mononuclear precursors of osteoclasts.

SUMMARY OF THE INVENTION

35 In a first aspect, the invention provides a nucleic acid molecule which comprises a sequence encoding a protein which

a) is expressed at least on osteoblasts, and
b) inhibits osteoclast differentiation from
haematopoietic cell precursors,

or which hybridises to said nucleic acid molecule
5 under stringent conditions. Suitable stringent conditions
are well known in the art. See the well known textbook by
Sambrook et al (1989), and Example 2 herein.

The nucleic acid may be cDNA, genomic DNA or
messenger RNA. Preferably the nucleic acid molecule is a
10 cDNA. More preferably the cDNA comprises a sequence
selected from the group consisting of SEQ ID NO: 2, SEQ ID
NO: 4, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID
NO: 10 and SEQ ID NO: 11.

Preferably the protein inhibits differentiation
15 of haematopoietic stem cells to osteoclast progenitor
cells. In a particularly preferred embodiment, the nucleic
acid molecule of the invention comprises a 110 base pair
sequence as set out in SEQ ID NO: 2.

This aspect of the invention also encompasses
20 anti-sense sequences directed against the nucleic acid
molecule defined above, and particularly encompasses an
anti-sense sequence directed against SEQ ID NO: 10.
Preferably the anti-sense sequence is SEQ ID NO: 24 or SEQ
ID NO: 25.

25 In a second aspect, the invention provides a
polypeptide encoded by the nucleic acid molecule of the
invention. Preferably the polypeptide is encoded by the
human cDNA sequence. More preferably the polypeptide
comprises an amino acid sequence encoded by SEQ ID NO: 20.

30 In a third aspect, the invention provides an
antibody directed against a polypeptide of the invention.
Preferably the antibody is directed against an epitope
present in the sequence

35 H-Cys-Met-Arg-Thr-Glu-Ala-Gln-Leu-Ala-Arg-Phe-Asp-Asn-Gln-
Asp-Glu-Leu-Asn-Phe-OH (SEQ ID NO: 26).

The antibody may be polyclonal or monoclonal, but is preferably monoclonal. Suitable methods for generating either polyclonal or monoclonal antibodies are very well known in the art. It will be clearly understood that the invention encompasses biologically-active fragments and analogues of such antibodies, including but not limited to ScFv fragments, trimeric antibodies, humanised antibodies and the like. Again, methods for producing such active fragments and analogues are well known in the art. See for example PCT/AU93/00491 and PCT/AU97/00212 and references cited therein.

In a fourth aspect, the invention provides a composition comprising a polypeptide or an antibody of the invention, together with a pharmaceutically-acceptable carrier.

Methods and pharmaceutical carriers for preparation of pharmaceutical compositions are well known in the art, for example as set out in textbooks such as Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pennsylvania, USA.

In a fifth aspect, the invention provides a method of treatment of a condition characterised by abnormal bone resorption, comprising the step of administering an effective amount of a modulator of expression or function of the polypeptide of the invention.

Where the condition involves excessive bone resorption, the method will comprise administration of the polypeptide of the invention or the nucleic acid encoding this polypeptide, or a biologically-active fragment or analogue thereof. Such conditions include, but are not limited to, osteoporosis, primary hyperparathyroidism, Paget's disease, rheumatoid arthritis, renal osteodystrophy, humoral hypercalcaemia of malignancy, and conditions where cancer has metastasised to bone.

Conditions characterised by deficient bone resorption include osteopetrosis. Antibodies directed against the polypeptide of the invention or anti-sense

oligonucleotides directed against the nucleic acid of the invention may be used to inhibit the function of the polypeptide and thus to increase bone resorption.

It is also contemplated that the polypeptide of the invention may be used to promote healing of bone fractures, particularly in individuals where fracture healing is delayed or deficient. These include individuals suffering from osteoporosis or diabetes mellitus.

In a sixth aspect, the invention provides a diagnostic kit, comprising a reagent selected from the group consisting of a nucleic acid of the invention or a fragment thereof capable of hybridising to a nucleic acid of the invention; an anti-sense nucleic acid of the invention; a polypeptide of the invention, and an antibody of the invention. For example, diagnostic kits for use in methods such as polymerase chain reaction, fluorescent *in situ* hybridisation, immunoassay, and the like are contemplated. Where appropriate, the molecule of the invention which is used may be labelled with a detectable marker, such as a radioactive, fluorescent, chemoluminescent or enzymic marker. Such diagnostic kits are useful for detection of abnormalities in the structure, expression or control of the factor of the invention, which may lead to increased bone resorption and concomitant pathological manifestations.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 summarises the factors and mechanisms involved in control of osteoclast differentiation and development, as understood before the date of the present invention.

Figure 2 shows detection by Northern blotting of a 780 base pair mRNA species using rOCIL323 as a probe in a variety of rat clonal osteoblast-like cell lines.

5 Figure 3 shows the results of Northern blot analysis using rOCIL402, a 402 base pair fragment obtained by screening of a rat ROS 17/2.8 cDNA library, using the polymerase chain reaction. Similar results were obtained using rOCIL323 fragment as a probe.

10 Figure 4 shows the comparison of rOCIL323 and rOCIL402 probes in Northern blotting of mRNA from 1,25-dihydroxyvitamin D₃-treated rat UMR 106-06 cells. The results showed that both fragments detected the same species of mRNA.

15 Figure 5 shows the results of Northern blot analysis of UMR 201 mRNA using mOCIL 2kb, showing that this probe detected the same 780 bp species as rOCIL323 and rOCIL402.

Figure 6 shows the intron-exon structure of the mouse OCIL gene

20 Figure 7 shows sequence comparisons between human, rat and mouse OCIL, as generated using the program Clustal W. Regions of sequence identity are shown shaded and in bold.

25 Figure 8 shows comparisons between the deduced protein sequence corresponding to hOCIL and the deduced protein sequences corresponding to rOCIL 1.3 and mOCIL, as generated using the program Clustal W.

30 Figure 9 shows the results of treatment of cocultures of primary mouse calvarial osteoblasts and mouse bone marrow cells with an anti-sense oligonucleotide, 323 A/S, directed against the C-type lectin region of OCIL and a second antisense oligonucleotide, 474 A/S, which was directed against the sequence in the open reading frame but outside the C-type lectin region.

35 a: cocultures treated with anti-sense oligonucleotide under basal conditions.

b-d: cocultures stimulated with anti-sense oligonucleotides in the presence of 1,25-dihydroxyvitamin D₃ and PGE₂.

Figure 10 shows the results of Northern blot analysis of mRNA from UMR106 parental cells, demonstrating upregulation of expression of OCIL by IL-1 α , IL-1 β , IL-11, IL-17, TNF α , TGF β , M-CSF, GM-CSF, PGE₂, 1,25-dihydroxyvitamin D₃, 1,25-dihydroxyvitamin D₃ plus PGE₂, and PGE₂ plus dexamethasone.

Figure 11A shows the results of a time-course study, showing upregulation of OCIL by PTHrP.

Figure 11B shows that the upregulation could be detected using either rOCIL402 or mOCIL 2kb as the probe.

Figure 12 shows upregulation of expression of OCIL in primary mouse calvarial osteoblasts by IL-1 α , IL-1 β , IL-11, dexamethasone, and 1,25-dihydroxyvitamin D₃.

Figure 13A shows upregulation of expression of OCIL in ST2 mouse stromal cells by PGE₂, dexamethasone, 1,25-dihydroxyvitamin D₃, IL-11, PTH, and 1,25-dihydroxyvitamin D₃ plus PGE₂.

Figure 13B shows the time course of upregulation of OCIL expression in ST2 cells by dexamethasone.

Figure 14 shows the results of Northern blot analysis of adult mouse tissues (left panel) and adult rat tissues (right panel), demonstrating expression of OCIL.

Figure 15 shows the effect of recombinant rOCIL protein on formation of multinucleate osteoclasts from mouse calvarial osteoblasts.

30 DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in detail by way of example only, with reference to the following non-limiting examples and drawings.

We set out to clone a gene encoding a peptide that would function to prevent osteoclast formation. It is known that mature osteoblasts have limited potential to support osteoclast formation, and we postulated that mature

osteoblasts might express osteoclastogenic inhibitors. The pre-osteoblastic cell line UMR201 can be differentiated to a more mature osteoblastic phenotype by treatment with 10^{-6} M retinoic acid for 24 hr (Ng et al, 1988). mRNA species differentially expressed between mature osteoblasts (retinoic acid-treated UMR201 cells) and immature osteoblasts (untreated UMR201 cells) were identified using an array of oligonucleotide primers in reverse transcription PCR, where products amplified from RNA from the two cellular populations were compared. We characterised products which were elevated in mature osteoblasts as candidates for osteoclastogenic inhibitory molecules.

Abbreviations used herein are as follows:

15	GM-CSF	granulocyte/macrophage colony stimulating factor
	hPTH	human parathyroid hormone
	IGF	insulin like growth factor
20	IL	interleukin
	LIF	leukaemia inhibitory factor
	M-CSF	macrophage colony stimulating factor (CSF-1)
	1,25(OH) ₂ D ₃	1,25-dihydroxyvitamin D ₃
	OCIF	osteoclastogenesis inhibitory factor
25	ODF	osteoclast differentiation factor
	OPG	osteoprotegerin
	PCR	polymerase chain reaction
	PGE ₂	prostaglandin E ₂
	PTH	parathyroid hormone
30	PTHrP	parathyroid hormone-related protein
	RANK	Receptor activator of NF- κ B
	TGF	transforming growth factor
	TNF	tumour necrosis factor
	TRAP	tartrate-resistant acid phosphatase.
35	<u>Example 1</u>	<u>Isolation of Rat cDNA Encoding the Inhibitory Factor</u>

Total RNA was isolated from retinoic acid-treated preosteoblastic UMR201 cells using guanidine thiocyanate (Chomczynski et al, 1987). First strand cDNA was synthesised from 2 µg of total RNA by incubating for 1 h at 42°C with 15 units of AMV reverse transcriptase (Promega, Madison, WI) following oligo dT priming. A sense primer that was complementary to rat calcitonin cDNA, designated primer CT1 (SEQ ID NO:1),

10 CT1 5'-ATG CTG GGC ACG TAC ACA CAA-3'

and 3'UAP 5'-CUA CUA CUA CUA GGC CAC GCG TCG ACT AGT AC-3' (Clontech) were used as primers in polymerase chain reaction (PCR). The PCR conditions utilised a touchup PCR protocol with denaturation at 94°C for 5 min, and then 5 cycles at 94°C for 1 min, 37°C for 1 min and 72°C for 1 min, followed by 35 cycles of 94°C 1 min, 49°C for 1 min and 72°C for 1 min. For these experiments, Expand High Fidelity PCR System (Boehringer Mannheim) was used in a Perkin Elmer Cetus 480 thermal cycler. A 321 bp PCR product was obtained. This 321 bp fragment, which we designated rOCIL323 (SEQ ID NO: 2), was used as a probe in Northern blots. As shown in Figure 2, it hybridised to a 780 bp mRNA species in UMR 201, UMR 201-10B, UMR 106-06, UMR 106-01 and ROS 17/2.8 cells, all of which are rat clonal osteoblast-like cell lines.

Since retinoic acid and PTH enhance OCIL mRNA expression dramatically in UMR 106-06 and UMR 106 parental cells, a similar RT-PCR procedure was carried out using RNA isolated from retinoic acid or hPTH 1-34 treated UMR 106 parental cells. A PCR product identical to the 321 bp fragment for rOCIL323 was obtained and its expression was found to be upregulated in UMR 106 cells treated with either retinoic acid or hPTH 1-34.

35 To extend the sequence of OCIL, anchored PCR was used to screen a rat ROS 17/2.8 cDNA library with λgt11

arms. An antisense 21 bp primer, designated OCILr1 (SEQ ID NO: 3),

OCILr1 5'-TGA GTG TTG TCT GTC CAC TTC CAA G-3'

5
complementary to a sequence in the 321 bp fragment, was used with either the λ gt11 forward primer 5'-GGT GGC GAC GAC TCC TGG AGC C-3' or λ gt11 reverse primer 5'-GAC ACC AGA CCA ACT GGT AAT G-3' (Clontech) to amplify an aliquot (10^6 plaque forming units) of the recombinant library. Cycling parameters were 94°C for 5 min, then 80 cycles of 94°C for 30 sec, 60°C for 30 sec, and 72°C for 2 min, followed by a final extension step of 72°C for 10 min. A 402 bp fragment was obtained with λ gt11 reverse primer as the anchored primer. Sequencing of this 402 bp fragment showed 88.6% identity over a length of 97 bp with rOCIL323 (SEQ ID NO: 2). The 402 bp fragment, designated rOCIL402, whose sequence is set out in SEQ ID NO: 4, was used to probe Northern blots obtained from the rat osteoblast-like cell line. It hybridised to the same 780 bp mRNA species observed with the rOCIL323 probe. These results are shown in Figures 3 and 4. The same results were obtained in both the presence and absence of 1,25-dihydroxyvitamin D₃.

25 A 3' Rapid Amplification of cDNA Ends (3'-RACE) strategy was used to obtain the 3' ends of the cDNA of interest. The sense specific primers used were OCILr11 (SEQ ID NO: 5)

30 OCILr11 5'-GAA ACA TCC CCC TGG AGT ATC C-3'

and OCILr12 (SEQ ID NO: 6)

OCILr12 5'-CCA AGT AAC TGG ACA TTG AGC CAG A-3'

35 complementary to sequences within rOCIL402 (SEQ ID NO: 4). First-strand cDNA was synthesised from total RNA isolated

from hPTH 1-34 treated UMR 106 parental cells, using the oligo dT-anchor primer. The cDNA was further amplified by PCR using OCILr11 or OCILr12 and the 3' adaptor primer AP-1 (Clontech). PCRs were run at 94°C for 5 min, then 35 cycles of 94°C for 30 s, 62°C for 30s, and 72°C for 2 min, followed by a final extension step of 72°C for 10 min. Three different polyadenylated 3' sequences were obtained, designated rOCIL1.3kb (SEQ ID NO: 7), rOCIL738bp (SEQ ID NO: 8) and rOCIL620bp (SEQ ID NO: 9) respectively. The region of sequence identity between rOCIL323 and rOCIL402 was found to extend to 117 bp.

Example 2 Isolation of Mouse cDNA and gDNA Encoding the Inhibitory Factor

ROCIL402 was labelled with [³²P] α-dCTP by using the Random Primer labelling kit (Boehringer Mannheim), and a mouse liver cDNA library was subjected to hybridisation screening at 65°C in a hybridisation buffer containing 4 x SSPE (SSPE contains 0.15 M NaCl, 0.01 M NaH₂PO₄, and 0.001 M EDTA), 5 x Denhardt's solution, 0.5% sodium dodecyl sulfate (SDS) for 24 hr. The filters were then washed sequentially in 2 x SSC at 65°C for 15 min, 2 x SSC with 0.1% SDS at 65°C for 30 min, and finally 0.1 x SSC at 65°C for 10min. We obtained a 1907bp mouse cDNA, designated mOCIL2kb (SEQ ID NO: 10). The sequence of mOCIL2kb shows 80% identity over a length of 461 bp to that of rOCIL1.3kb. When used as an antisense riboprobe in Northern blot analysis, mOCIL2kb hybridised to a 780 bp mRNA species in UMR201 as detected by rOCIL323 and rOCIL402, as shown in Figure 5.

A cDNA fragment corresponding to the nucleotides 58-776 of mOCIL2kb was used as a cDNA probe to screen a genomic BAC Mouse I Hybridisation library. The screening α was performed under contract by Genome Systems, Inc. According to their protocol, the cDNA fragment was labelled with [³²P] α-dCTP by random primer labelling and the library was screened under the hybridisation condition of

55°C in a hybridisation buffer containing 5.5 x SSC, 5 x Denhardt's solution, 0.5% SDS and 0.5 x HEPES buffer for 18 hr. The filters were then washed sequentially in 1mM Tris-HCl pH 8.0 and 1% sarkosyl for 15 min, and 3 times in 1mM Tris-HCl pH 8.0 for 15 min washes at room temperature. Eight positive clones were isolated, of which four positive clones were screened. After the genomic DNA was digested with HindIII or BamHI, Southern blot analyses were carried on with the same cDNA probe. The results showed that two clones were identical, and one clone could not grow in culture. One of the duplicate clones, designated db.20149, was sequenced by subcloning into the pBS vector and by direct sequencing of the genomic clone using cycle sequencing. Sequencing of 9349 bp of the genomic clone of mOCIL was completed (SEQ ID NO: 11). It contains 6 exons, as shown in Figure 6. The 5' flanking region adjacent to exon I is a GC-rich region, containing a Sp 1 binding site. A 1 kb gap between nucleotides 1862 and 1868 is currently being sequenced. The genomic sequence confirmed that nucleotides 1-320 of the original mOCIL2kb represented an inverted repeat of the 3' end of the sequence, and that nucleotides 900-1907 of mOCIL2kb were not part of the mOCIL sequence. The corrected full length mOCIL cDNA is 990 bp in length (SEQ ID NO: 12).

To confirm the mOCIL cDNA sequence, RT-PCR was carried out using total RNA isolated from ST2 mouse stromal cells, primary mouse calvarial osteoblasts and mouse liver tissue. The sense primer represented nucleotides 18-36 of mOCIL and is designated as primer OCILm47 (SEQ ID NO: 13),

30

OCILm47 5'- TCC CAT GCC AGA TTG CTT G-3'

The antisense primer represented nucleotides 743-720 of mOCIL and is designated primer OCILm12 (SEQ ID NO: 14),

35

OCILm12 5'-GGG ACC ATA GGG GAA AAA GTA G-3'

The PCR was run at 94°C for 5 min, then 35 cycles of 94°C for 30s, 60°C for 30s, and 72°C for 1 min, followed by a final extension step of 72°C for 10 min. Five clones
5 containing a 721 bp fragment were obtained from three sources, ST2 mouse stromal cells, primary mouse calvarial osteoblasts and mouse liver tissue. When compared to the mOCIL sequence there was 100% identity in the first 106 bp (exons I and II) but only 90.5% identity in the remaining
10 615 bp. This 721 bp fragment was designated as mOCIL47 (SEQ ID NO: 15).

To confirm whether nucleotides 320-434 of mOCIL2kb are part of mOCIL, a sense primer representing nucleotides 343-364 of mOCIL2kb, designated as primer
15 OCILm17 (SEQ ID NO: 16),

OCILm17 5'-TGG AAA CTC AGC TCC TCA GCT CTG-3'

and antisense primer OCILm12 was used to carry out RT-PCR
20 with RNA from three sources, ST2 mouse stromal cells, primary mouse calvarial osteoblasts and mouse liver tissue, as above. PCR was run under the same conditions as for mOCIL47. Twelve clones were obtained, each containing a 713 bp fragment. The first 115 bp were not identical to
25 mOCIL. In 2 of the 12 clones, there was 100% identity to mOCIL after the first 115 bp. In the other 10 clones, there was 92.2% identity to mOCIL and 89.2% identity to mOCIL47 after the first 115 bp. This sequence is designated mOCIL17 (SEQ ID NO: 17).

30 RT-PCR was also carried out using a sense primer corresponding to the region located at the junction of exon III and exon IV, representing nucleotides 243-267 of mOCIL, and designated primer OCILm32 (SEQ ID NO: 18),

35 OCILm32 5'- TTT GTC AGC AAC AAA GAC AGA ACA G-3'

Primer OCILm12 was used as a antisense primer. RT-PCR was carried out with RNA from three sources, ST2 mouse stromal cells, primary mouse calvarial osteoblasts and mouse liver tissue, as above. PCR was run under the same conditions. Four clones were obtained, each containing a 502 bp fragment. Three of the four clones have 100% identity to mOCIL17 and one of the four clones is 100% identical to mOCIL.

mOCIL has an open reading frame encoding a 218 amino acid protein. Its structure is typical of a type II membrane protein, with a predicted 142 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 55 amino acid cytoplasmic domain. The extracellular domain has 6 cysteine residues. There are three potential N-linked glycosylation sites at residues 86, 112 and 207, all of which are in the extracellular domain. There is a myristylation motif in the intracellular domain.

Comparison of the putative protein sequences derived from the rOCIL323, rOCIL1.3kb and mOCIL cDNA sequences with the SwissProt protein database indicated that the mOCIL protein sequence included an 80 amino acid C-lectin type motif, from positions 92 to 171 in the mOCIL protein sequence. This C-lectin motif is similar to that of CD69, a membrane-bound lectin expressed by bone marrow haematopoietic cells, and thought to be involved in monocyte differentiation. C-lectin motifs are also involved in cell-cell contact and lipid binding (Sharon and Lis, 1995; Gabius 1997; Kieda, 1998). MOCIL47 shows 100% identity to a cDNA clone encoding a C-type lectin expressed in bone marrow cells, which was deposited in the Gen Bank data base on 29 March 1999 (Accession No. AF121352). The full length mOCIL cDNA (SEQ ID NO:12) is 92% homologous to this.

The three different sequences (SEQ ID NO: 12, 15 and 17), which overall have 90% identity, may represent gene duplications, where either one or all three sequences may have similar biological outcomes. The functional data

we have to date, relating to the inhibition of osteoclast formation from haemopoietic precursor cells using antisense oligonucleotides (SEQ ID NO: 1 and 13), have been obtained mainly with mOCIL17 (SEQ ID NO: 7).

5

Example 3 Isolation of Human cDNA Encoding the
Inhibitory Factor

[³²P] α-dCTP labelled rOCIL402 was used to probe a human fetal cDNA library under low stringency hybridisation conditions at 55°C in a hybridisation buffer containing 4 x SSPE, 5 x Denhardt's solution, 0.5% SDS for 24 hr, and then washed with low stringency at 2 x SSC with 0.1% SDS at 40°C for 15 min, and 1 x SSC/0.1% SDS at 40°C for 15min. Eight positive clones were obtained after tertiary screening. Clone No. 6 is a 1.3 kb cDNA segment, whose sequence was designated hOCIL (SEQ ID NO: 19). The putative protein sequence encoded by bp883-1059 was a C-type lectin moiety, which showed 73% homology to the C-type lectin sequence previously demonstrated in rOCIL323, rOCIL1.3kb and mOCIL2kb. However, regions of amino acid sequence 5' and 3' to this C-type lectin domain were different from those of the mouse and rat sequences, as shown in Figure 6.

Clone No. 8 is 960 bp long. It has a 64% identity over a length of 145 bp with rOCIL402. A search of the EST database showed that clone No. 8 has 99.5% sequence identity with a human EST clone. Accession No. AA029932, over a published length of 209 bp. This EST clone was ordered and further sequenced. The EST clone is 680 bp in length, and has 64% identity with rOCIL1.3kb over a length of 343 bp. It also has 64% identity over a length of 346 bp compared to mOCIL. RT-PCR showed that clone NO. 8 and AA029932 represent overlapping clones, which are contiguous, and combine to represent a human OCIL (hOCIL) of 1336 bp in length (SEQ ID NO: 20).

The deduced protein sequence showed 56% homology to the deduced protein sequence of rOCIL1.3kb, and 62%

homology to that of mOCIL, as shown in Figure 7. These differences are principally at the N-terminal. Although there is 80% homology between the mouse and human OCIL proteins in certain regions, this indicates that the mouse
5 cDNA could not reliably be used to isolate a human genomic DNA encoding hOCIL.

In order to obtain the hOCIL gene, the 680 bp cDNA insert of clone AA029932 was isolated and screened by Genome Systems, Inc. against the genomic BAC Human Release
10 II Hybridisation library, as described in Example 2. One positive clone was obtained and 7kb of this clone was sequenced. This sequence has 100% identity to a human genomic clone, which was deposited in the GenBank database on April 6, 1999 (Accession No. AC007068). These
15 sequences, when combined, indicate that the hOCIL gene is greater than 10 kb in length (SEQ ID NO: 21). The genomic sequences corresponding to the 5' flanking region, promoter region and the first 654 bp of cDNA sequences are not represented in the sequence deposited in Accession No.
20 AC007068.

The hOCIL gene is located in chromosome 12,12p. Chromosome 12 and chromosome 11 are considered to be evolutionarily related. There are several examples of evolutionarily
25 related proteins whose genes are located on chromosome 12 and chromosome 11 such as PTH and PTHrP, IGF and IGF I, Harvey ras sarcoma 1 and Kisten ras sarcoma 2 etc. (Martin et al., 1991). Thus chromosome 11 and chromosome 12 share genes of similar biological characteristics with redundant
30 function.

Example 4 Effect of Anti-Sense Oligonucleotides on Transcription

Primary mouse calvarial osteoblasts were
35 cocultured with mouse bone marrow cells to generate mononuclear and multinucleate osteoclasts. Staining for tartrate-resistant acid phosphatase (TRAP), performed using

a commercial leukocyte acid phosphatase kit from Sigma
Diagnostics (St. Louis, MO, USA) (Katsogiannis *et al*,
1998), identified these cells as osteoclasts. Under normal
conditions, multinucleate functional osteoclasts are not
5 formed unless the cocultures are stimulated with 1,25-
dihydroxyvitamin D₃ and PGE₂.

Experiments were carried out to block translation
of OCIL mRNA in order to determine the function of its
translated product. Primary mouse calvarial osteoblasts
10 were treated with antisense oligonucleotides. Four
antisense oligonucleotide sequences were designed. Two of
these antisense oligonucleotide sequences were
complementary to the C-type lectin region, and designated
323 (SEQ ID NO: 22) and 402 (SEQ ID NO: 23) respectively:
15

323 5'-GAG TGT TGT CTG TCC ACT TCC-3'

402 5'-TTT CCA ACT CCA ATC CAG TTT-3'

20 The 323 antisense oligonucleotide has 19 of 21 bp
complementary to mOCIL47.

25 5'-GAGTGTGTCTGTCCACTTCC-3' 323 antisense
||||||| |||||||||
3'-GTCACAACAAACAGGTGAAGG-5' mOCIL47 Strand +

and has 20 of 21 bp complementary to mOCIL and mOCIL17:
30

5'-GAGTGTGTCTGTCCACTTCC-3' 323 antisense
||||||| |||||||||
35 3'-GTCACAACAGACAGGTGAAGG-5' mOCIL17 Strand +

The 402 antisense oligonucleotide has 100% complementarity
to mOCIL and has 20 of 21 bp complementary to mOCIL47 and
mOCIL17:

5'-TTTCCAACCTCCAATCCAGTTT-3' 402 antisense
 |||||
 3'-AAAGGTTGAGGTCAGGTCAAA-5' mOCIL47 Strand +

5'-TTTCCAACCTCCAATCCAGTTT-3' 402 antisense
 ||| |||||
 3'-AAAAGTTGAGGTTAGGTCAAA-5' mOCIL17 Strand +

The other two antisense oligonucleotide sequences, respectively designated 439 (SEQ ID NO: 24) and 474 (SEQ ID NO: 25), specifically inhibit the translation of mOCIL17.

The oligonucleotide 439 is antisense to the sense primer OCILm17 and located upstream of the open reading frame:

439 5' GAG GAG CTG AGT TTC CAC TAC-3'

The antisense oligonucleotide 474 is complementary to a region in mOCIL17 in the open reading frame but outside the C-type lectin region:

474 5'-GGT AGG GAA GCC TTT GTG AC-3'.

Under basal conditions, ie. in the absence of stimulation with 1,25-dihydroxyvitamin D₃ and PGE₂, there was a 3- to 5-fold increase in the number of mononucleate TRAP-positive cells in the cocultures treated with the 323 and 474 antisense oligonucleotides over the period from 3 to 7 days. With the 402 antisense oligonucleotide, a 4.5-fold increase in the formation of mononucleate TRAP positive cells was observed after 7 days treatment. Multinucleate TRAP-positive cells (323; 4.5 ± 2, 474; 4.25 ± 1.25) were also observed in cocultures treated with both 323 and 474 antisense oligonucleotides at a concentration of 5µM, whereas none were observed in the

control. These experiments were performed three times, and a representative result is shown in Figure 9a.

When the cocultures were stimulated with 1,25-dihydroxyvitamin D₃ and PGE₂, multinucleate TRAP-positive osteoclasts were formed after 7 days. Treatment with 5 µM 323 antisense oligonucleotide resulted in a seven-fold increase in the number of multinucleate osteoclasts, as shown in Figure 9b.

Treatment with 10 µM 402, 5 µM 439 and 474 antisense oligonucleotide resulted in a 2 to 3-fold increase in the formation of multinucleate osteoclasts after 7 days, as shown in Figures 9c and 9d.

These TRAP-positive cells were further characterized as osteoclasts by the presence of receptors for calcitonin, demonstrated using autoradiography and immunostaining, and by the ability of these cells to form resorption pits in bone slices.

Effects of mOCIL antisense oligonucleotides on the three phases of osteoclast formation were also investigated. Mouse bone marrow and primary osteoblastic cells were cocultured in the absence of 1,25-dihydroxyvitamin D₃ and PGE₂ for a 7 day culture period. 323 and 474 antisense oligonucleotides were added for 3 phases of culture: the first phase (0-3 days), in which there is proliferation of osteoclast progenitors, the second phase (3-5 days) and the final phase (5-7 days), in which these cells differentiate into mature osteoclasts. TRAP-positive osteoclasts were counted. In order to examine the role of OCIL on the bone resorptive activity of mature osteoclastic cells, the cells were also cultured on dentine slices under the same culture conditions as above, and resorption pits formed on dentine slices were quantitated. The results are shown in Table 1, and indicate that the OCIL acted at an early stage in osteoclast formation.

Table 1
Effects of mOCIL Antisense Oligonucleotides on the Three Phases of Osteoclast Development

TIME	TREATMENT	MONO	MNC	PITS
7 days	control	3596 ± 511.5	0	10 ± 4.4
0-3 days	323	6880 ± 674 *	7.7 ± 5.3	34 ± 15
	474	6893 ± 429.6 **	8.7 ± 1.7 *	20 ± 2.5
3-5 days	323	2840 ± 197.6	0	14 ± 6
	474	3110 ± 334	4.3 ± 2	24 ± 2.5 *
5-7 days	323	4236 ± 518.6	0	10.6 ± 0.79
	474	3363 ± 139.8	0	3.3 ± 2
0-7 days	474	5223 ± 571 *	3.3 ± 1	20.3 ± 5.9

5

mono mononuclear osteoclast precursors
MNC multinucleate osteoclasts
pits resorption pits formed on dentine slices

*p < 0.05 vs. control

**p < 0.01 vs. control

Example 5 Regulation of expression of OCIL mRNA

The regulation of OCIL mRNA expression was examined in the UMR106 parental osteoblast-like cell line using rOCIL402 as a probe. As shown in Figure 10, expression of the mRNA was upregulated by retinoic acid (RA), parathyroid hormone (1-34), parathyroid hormone related protein (1-34), TNF- α , interleukin 1 α (IL-1 α), IL-1 β , IL-11, IL-17, GM-CSF, M-CSF, TGF β , dexamethasone, 1,25-dihydroxyvitamin D₃ and prostaglandin E₂. A time course study, illustrated in Figure 11, showed that parathyroid hormone-related protein (1-34) increased levels of OCIL mRNA as early as 1 hour, peaking at 4 hours and maintaining the high level of expression until 48 hours.

As shown in Figure 12, in primary mouse calvarial osteoblasts, OCIL mRNA was upregulated by IL-1 α , IL-1 β , IL-11, 1,25-dihydroxyvitamin D₃ and retinoic acid. In ST2 mouse stromal cells, OCIL mRNA was upregulated by dexamethasone, 1,25-dihydroxyvitamin D₃ and IL-11. The time course also showed that dexamethasone increased OCIL mRNA at 1 hour, peaking at 2 hours and returning a basal level at 24 hours. These results are illustrated in Figures 13A and 13B, respectively.

Example 6 Localization of OCIL mRNA

mRNA encoding OCIL was localised in fetal, newborn and adult mouse tissue by *in situ* hybridisation using the rOCIL 402 antisense probe, using a method described previously (Katsogiannis et al, 1997 and 1998). Plasmid cDNA was labelled with digoxigenin (DIG) using an RNA labelling kit (Boehringer-Mannheim, Mannheim GmbH, Germany). Hybridisation signals were detected by alkaline phosphatase staining with BCIP/NBT after incubation with an anti-digoxigenin antibody coupled to alkaline phosphatase. The mRNA is expressed in a range of tissues, as summarized in Table 2.

Table 2
Adult Rat Tissues Probed with rOCIL402

	Tissue	OCIL mRNA
Calvaria	Osteoblasts	+++
	Marrow hematopoietic cells	++
	Megakaryocytes	++
Kidney	Medulla (collecting tubules)	+++
	Outer cortex (collecting tubules only)	+
	Glomeruli (endothelial cells only weakly positive)	-ve
	Proximal/distal tubules	-ve
Lung	pneumocytes	++
	bronchial epithelium	++
Brain	Neurones in cerebral cortex, cerebellar cortex, hippocampus; choroid plexus	+++
Heart	Cardiac muscle	+++
Spleen	White pulp	+++
	Cortex	+
	Red pulp	-ve
Gut	Luminal epithelium	++
Liver	Hepatocytes	-ve

5

In situ hybridization was also carried out to detect OCIL mRNA localisation in adult rat tissue and human skin, using the same method, and the results are summarized in Table 3.

10

Table 3
Normal Murine Tissues Expressing OCIL mRNA

Tissues	Fetal (day 15)	Newborn (day 1)	Adult (5-8 weeks)
<i>Extraskkeletal tissues</i>			
Brain	+++	+++	+++
Lung	++	+++	-
Heart	+++	+++	++
Kidney	++	+++	-
(collecting tubules)			
Small Intestine	+	+	-
Liver	+/ (mk=++++) *	+	-
Skeletal muscle	+++	+++	++
Skin	+++	+++	++
Spleen	nd	nd	++
<i>Skeletal tissues/cells</i>			
Long bone			
chondrocytes	+++	++	+++
osteoblasts	na	+++	+++
osteoclasts	nd	++ or -	++ or -
perichondrium/	++	+++	++
periosteum			
marrow/megakaryocytes	na	++	++
Calvarial bone			
osteoblasts	+++	+++	++
osteoclasts	++	++	++
periosteum	nd	++	++

- 5 (+) denotes weak signal
 (++) denotes moderate signal
 (+++) denotes strong signal
 (-) denotes absence of signal
 (na) not applicable

(nd) not determined.

*(mk) megakaryoblast of fetal liver.

OCIL mRNA localization in human skin probed with OCIL402:

5

Epidermis (all layers)

+++

**Basal layer slightly weaker signal

10 In Northern blot analyses of adult mouse tissues
using mOCIL2 as the probe, OCIL mRNA was shown to be
expressed in heart, skin, lung, liver, kidney, gut and
brain. In adult rat, OCIL mRNA was found to be expressed
in brain, bone, lung, liver, gut, kidney, mouse, skin and
heart. These results are illustrated in Figure 14.

15

Example 7 Antibody Directed Against OCIL

The following peptide fragment of the deduced
amino acid sequence derived from the cDNA sequence of OCIL
was synthesized, and was used to immunize rabbits, using
20 standard protocols.

H-Cys-Met-Arg-Thr-Glu-Ala-Gln-Leu-Ala-Arg-Phe-Asp-Asn-Gln-
Asp-Glu-Leu-Asn-Phe-OH (SEQ ID NO: 26)

25

The antibody raised may be used to detect the
OCIL protein, using standard immunohistochemical methods,
or to neutralize OCIL activity in murine co-cultures to
stimulate osteoclast formation.

30 Example 8 Immunohistochemistry

A rabbit polyclonal antibody prepared as
described in Example 7 was used for immunohistochemistry.
A kit for the standard peroxidase-labelled streptavidin-
biotin detection method (DAKO, Boenisch, 1989) was used
35 according to the manufacturer's instructions with minor
modifications. The dilution of the antiserum used was
optimised in preliminary experiments. Incubation of tissue

sections with a 1:100 dilution of the primary antiserum was carried out overnight at 4°C in a humidified chamber. Peroxidase activity was detected with 3'-3'-diamino-benzidine tetrahydrochloride (Sigma) and 0.15% H₂O₂.

- 5 Slides were counterstained with haematoxylin, dehydrated and mounted on a coverslip. The results are summarized in Table 4.

Table 4
Normal Murine Tissues Expressing mOCIL protein

10

Tissues	Fetal (day 15)	Newborn (day 1)	Adult (5-8 weeks)
<i>Extraskkeletal tissues</i>			
Brain	nd	+	+++
Lung	nd	++	+
Heart	nd	++	++
Kidney (collecting tubules)	nd	++	++
Small Intestine	nd	nd	nd
Liver	nd	nd	nd
Skeletal muscle	nd	++	++
Skin	nd	++	++
Spleen	nd	nd	nd
<i>Skeletal tissues/cells</i>			
Long bone chondrocytes	nd	++	++
osteoblasts	na	+++	+++
osteoclasts	nd	nd	nd
perichondrium/periosteum	nd	++	++
marrow/megakaryocytes	na	++	++

(+) denotes weak signal;
(++) denotes moderate signal;
(+++) denotes strong signal;

(-) denotes absence of signal;

(na) not applicable;

(nd) not determined.

5 Example 9 Recombinant OCIL protein

OCIL proteins were prepared by recombinant DNA technology to allow more extensive laboratory studies of their actions on osteoclast formation as well as osteoblast function. Soluble mouse and rat OCIL cDNA tagged at the N-terminus with the FLAG epitope were constructed in the pEF-BOS Mammalian expression vector (Mizushima & Nagata 1990), which had been modified to contain an in-frame IL-3 signal sequence and FLAG peptide coding sequence (gift of Dr. D Hilton).

15 In order to obtain a RT-PCR product encoding the mOCIL extracellular domain (amino acids 77-218) to clone into the MluI site of the vector, as shown in Figure 6, the RT-PCR was carried out using total RNA isolated from primary mouse calvarial osteoblasts, which support
20 osteoclast differentiation in coculture. A sense primer, OCILm33, comprising OCILm32 representing nucleotides 243-267 of mOCIL and containing a MluI site, designated primer OCILm33 (SEQ ID NO: 27):

25 OCILm33 5'-GCC ACG CGT TTG TCA GCA ACA AAG ACA GAA CAG-3'

and an antisense primer comprising OCILm12 (SEQ ID NO: 4), representing nucleotides 743-720 of mOCIL and containing a MluI site, designated primer OCILm46 (SEQ ID NO: 28),

30 OCILm46 5'-GCC ACG CGT GGG ACC ATA GGG GAA AAA GTA G-3'

were used as primers in the PCR. PCR was run at 94°C for 5 min, then 35 cycles of 94°C for 30 s, 60°C for 30s, and
35 72°C for 1 min, followed by a final extension step of 72°C for 10 min. A 501 bp fragment was obtained and further cloned into the expression vector pEF-BOS. The open

reading frame and FLAG fusion was confirmed by sequencing (bp 1-132), and the 501 bp fragment sequence (SEQ ID NO: 29) was confirmed to be identical to mOCIL17.

To obtain a PCR product encoding the rOCIL1.3kb extracellular domain (amino acids 40-179), a sense primer to represent nucleotides 126-146 of rOCIL1.3kb with the MluI site, designated primer OCILr22 (SEQ ID NO: 30),

OCILr22 5'- GCC ACG CGT TCA GTA AAA AAG ACA GCC AAG-3'

and an antisense primer representing nucleotides 544-526 of rOCIL1.3kb with the MluI site, and designated primer OCILr23 (SEQ ID NO: 31),

OCILr23 5'-GCC CAG CGT AAC TAC AGG CAC TGT GAG G-3'

were used as primers in a PCR. PCR was carried using rOCIL1.3 kb plasmid as template and run at 94°C for 5 min, then 35 cycles of 94°C for 30 s, 60°C for 30s, and 72°C for 1 min, followed by a final extension step of 72°C for 10 min. A 421 bp fragment was obtained and cloned into the expression vector pEF-BOS. The open reading frame and FLAG fusion were confirmed by sequencing.

HEK 293 cells were transfected with both mouse and rat expression constructs using Lipofectamine (Life Technologies, Inc). Supernatant was harvested after 72 hours. The recombinant protein was purified by incubation with the anti-FLAG M2 affinity gel (Kodak), and eluted with the FLAG peptide (Kodak) as outlined in the manufacturer's protocol. The purified protein was used to study its effects on osteoclast formation in murine cocultures.

An experiment was also carried out to determine the action of rOCIL protein in osteoclast formation.

Primary mouse calvarial osteoblasts were cocultured with mouse spleen cells obtained from 15 week-old mice and stimulated with 1,25-dihydroxyvitamin D₃ and PGE₂ in the

presence of rOCIL protein for 10 days. A negative control was carried out as with protein carrier buffer alone. As shown in Figure 15, rOCIL protein significantly reduced the number of osteoclasts formed when compared to the presence of carrier buffer alone.

DISCUSSION

We conclude from our experiments that in osteoblasts OCIL is expressed on the cell surface as a type II membrane peptide. Contact with haematopoietic precursor cells prevents further differentiation into mononucleate osteoclast precursors, and ultimately into functional multinucleate osteoclasts. Without wishing to limit the scope of the invention by any proposed mechanism, we consider that upregulation of OCIL mRNA expression by the same osteotropic factors that increase expression of ODF is consistent with the hypothesis that regulation of bone resorption by osteoclasts is tightly regulated. According to this hypothesis, stimulation of multinucleate osteoclast formation through ODF would simultaneously prevent the generation of new osteoclasts through the action of OCIL. If this system is operative under normal physiological conditions, then bone resorption becomes a self-limiting process.

In vivo, OCIL has the potential to be used as a therapeutic agent in the treatment of conditions which are characterised by excessive bone resorption, such as osteoporosis, primary hyperparathyroidism, Paget's disease, rheumatoid arthritis, renal osteodystrophy, and humoral hypercalcaemia of malignancy, as well as metastatic bone disease. Modulation of the expression or function of the factor may also be useful in the treatment of disorders involving extra-skeletal calcification.

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding,

various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

5

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SEQUENCE ID LISTING

(1) GENERAL INFORMATION:

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5 (A) NAME: ST VINCENT'S INSTITUTE OF MEDICAL
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10 (E) COUNTRY: AUSTRALIA

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(ii) TITLE OF INVENTION: INHIBITOR OF OSTEOCLAST
PRECURSOR FORMATION

15

(iii) NUMBER OF SEQUENCES: 31

(iv) COMPUTER READABLE FORM:

20 (A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version
#1.30 (EPO)

25 (2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

35

ATGCTGGGCA CGTACACACA A

21

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 321 base pairs

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

CGCTCTAGCC CGGCCACGCG TCGACTAGTA CAGCTCCAAA TCTGTGCCCC
TCAGTTCCTC 60

15 CCTCCTGTTA TCTCTAGAGG AAGCTGTGGA GAGATTCCAG GATCATCTGA
AACAGAGACA 120

CATGCATTCT CGGCTTTTTG TGTTTTATTA CAGAATTTCT TAAGCAGATA
CAAAGGGAGT 180

20 TTTGATTACT GGATCGGCCT GCACAGAGAG TCCTCAGAGC ACCCTTGGA
GTGGACAGAC 240

AACACTCAGT ATAACTACTC GTATGTTTCA CAATGTTTTT TCTTCTACTG
25 TGTTTCATGTC 300

TTGTTGAGGT CTTGTGTGTA C 321

30 (2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

5 TGAGTGTGTG CTGTCCACTT CCAA 24

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 402 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

15 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

20 ACAGTAAAAT GCTCCAAGGA AAGCTTCCCA GAAACATCCC CCTGGAGTAT
CCTGCTGGGC 60

CTTACTGCTG CTACGTAGTG ATCATTGTCC TCAGTGTTAG CTGTAGTTCT
CTTTCTGTTG 120

25 CTTTGTTCAGT AAAAAAGACA GCCAAGATCT CAACCATAAA TACTTATGCT
GCTTGCCCCG 180

GAAACTGGAT TGGAGTTGGA AATAAATGTT TTTATTTTAA TGAAATACCA
AGTAACTGGA 240

30 CATTGAGCCA GACCCTCTGT AAGGAACAAG GGGCCGAGCT AGCACGATTT
GACACCGAGG 300

35 AGGAGCTGAA TTTCCTAAGG AGATACAAAG GGAGTTCAGG TTACTGGTCC
GGTCTGCACA 360

GAGAGTCATC AGCGCACCCCT TGGAAGTGGG CAGACAACAC TC 402

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GAAACATCCC CCTGGAGTAT CC

22

15 (2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

25

CCAAGTAACT GGACATTGAG CCAGA

25

(2) INFORMATION FOR SEQ ID NO: 7:

30 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1302 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

ACAGTAAAT GCTCCAAGGA AAGCTTCCA GAAACATCCC CCTGGAGTAT
CCTGCTGGGC 60
5
CTTACTGCTG CTACGTAGTG ATCATTGTCC TCAGTGTTAG CTGTAGTTCT
CTTTCTGTTG 120
CTTTGTCAGT AAAAAAGACA GCCAAGATCT CAACCATAAA TACTTATGCT
10 GCTTGCCCCGA 180
GAAACTGGAT TGGAGTTGGA AATAAATGTT TTTATTTTAA TGAAATACCA
AGTAACTGGA 240
15 CATTGAGCCA GACCCTCTGT AAGGAACAAG GGGCCGAGCT AGCACGATTT
GACACCGAGG 300
AGGAGCTGAA TTCCTAAGG AGATACAAAG GGAGTTCAGG TTACTGGTTC
GGTCTGCACA 360
20 GAGAGTCATC AGCGCACCCCT TGGAAGTGGA CAGACAACAC TGAGTATAAC
AACTCGGTTT 420
CCATCGGAGG AGATGAAAAA CATGGCTTCC TGAGTGACAA TGGGTTTCAGC
25 AGTGGCAGGG 480
GTTATATAGT GAGGAAGTCG ATTTGTAGGA AGCCCAACAG CTACACCTCA
CAGTGCCTGT 540
30 AGTTTTGTGT CCTTG GTTGA GACTTTGTCC TAACAGTCAT GAGGAACACA
GAACATGGTA 600
TCTACAGTGC CTGAATCATG AACAATCTGC TAAAATCATC TTCAATTTCAT
AATGTGTGGT 660
35 GACATCTAAG ATAACAAGT AGGCATATTT TGCTTGGGAG ATCATGAATT
GTTCTATATT 720

AAATAGGTAT TCAGGTATGA GCTGGTTCTC ACATCTTAAA CATAAACTGA
ATCATGTCAG 780

5 TATTAGTTAT CTCTACTTTC TTTTTTCTCT CATTTAAATT ATATTATTTA
TTTATATTCC 840

AAATACCGTC CCTCCTTGT TCCCCCTTCT AGAGTTGTTT ACTCCATACC
CCTTCATCTT 900

10

TACTTCTGAA GAGATGTTCC CCCACCCAC TCTGAGTATT TCCCTTCTCT
TGGACTTTAG 960

GACTGTACAG GATTAGGTGC ATCCTCTCAT AGTGAGGCCA ACTGTAGGGA
15 GCTGCGACAT 1020

GCCGTGCCTC AAAATGGTGC TGGTTTCCGC CTTCCACCCT CCCAACAGTG
AGCGCTCCTT 1080

20 GTAGTAAACA AGTCCTTATT TGACTATGCC TGCCTGGCCT GCTAGGTTCA
GCATAGTGAC 1140

AGCCTGTCTG CATGACCCAT GTGGCACGTT GGGGTTGGTT GGTGTTGGAT
ACATAAGCTG 1200

25

ATGTAGGGCA TTCCCCTGGG GTAGTAGATG ATTGTATCAA GGTTCCTGAA
TAAACTGCTT 1260

GAAGAAAAAA AAAAAAAAAA AAGTACTAGT CGACGCGTGG CC 1302
30

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

- 35 (A) LENGTH: 738 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

AGTAAAATGC TCCAAGGAAA GCTTCCCAGA AACATCCCCC TGGAGTATCC
TGCTGGGCCT 60

10 TACTGCTGCT ACGTAGTGAT CATTGTCCTC AGTGTTAGCT GTAGTTCTCT
TTCTGTTGCT 120

TTGTCAGTAA AAAAGACAGC CAAGATCTCA ACCATAAATA CTTATGCTGC
TTGCCCCGAGA 180

15 AACTGGATTG GAGTTGGAAA TAAATGTTTT TATTTTAATG AAATACCAAG
TAACTGGACA 240

TTGAGCCAGA CCCTCTGTAA GGAACAAGGG GCCGAGCTAG CACGATTTGA
20 CACCGAGGAG 300

GAGCTGAATT TCCTAAGGAG ATACAAAGGG AGTTCAGGTT ACTGGTCCGG
TCTGCACAGA 360

25 GAGTCATCAG CGCACCCTTG GAAGTGGACA GACAACACTC AGTATAACTA
CTCACAGAGC 420

CTCAGATGGG GAGCCGGGAC TCTGAAATCC CAGAAAGCCA CTGCAGAACT
GCAAGCCTGA 480

30 GATTTTGATG TCCACTATTT GCATGGCTGC ACCTGTTTCAG GAAAGCAGAG
ATTTTAAGGA 540

CATTCGGAAC CTCCTTTAAA GTTTTGTCAT CACAGAGCAC CCAAAACAGT
35 CCTCGAATCA 600

CAGGCCCACT CCCATCCACC GTTAAAGCAC CTTTGAGCAA TTTAATAAGA
AGTGCGTGTT 660

CCCATGTGTA AAATGAATAA AAACAGAATT GGAAAAAAAA AAAAAAAAAA
5 AAAAAAAAAA 720

AAAAAAAAAA AAAAAAAAAA 738

10 (2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 620 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

20

AGTAAAATGC TCCAAGGAAA GCTTCCCAGA AACATCCCCC TGGAGTATCC
TGCTGGGCCT 60

25

TACTGCTGCT ACGTAGTGAT CATTGTCCTC AGTGTTAGCT GTAGTTCTCT
TTCTGTTGCT 120

TTGTCAGTAA AAAAGACAGC CAAGATCTCA ACCATAAATA CTTATGCTGC
TTGCCCCGAGA 180

30

AACTGGATTG GAGTTGGAAA TAAATGTTTT TATTTTAATG AAATACCAAG
TAACTGGACA 240

TTGAGCCAGA CCCTCTGTAA GGAACAAGGG GCCGAGCTAG CACGATTTGA
CACCGAGGAG 300

35

GAGCTGAATT TCCTAAGGAG ATACAAAGGG AGTTCAGGTT ACTGGTCCGG
TCTGCACAGA 360

GAGTCATCAG CGCACCCTTG GAAGTGGACA GACAACACTC AGTATAACTA
CTCGCTTTCC 420

5 ATCCGGGGAG TGGAAAGATA TGCCTACCTG AACGACATCG GGATCAGCAG
TGCCAGGGTC 480

TATGCAGACA AAAGATGGAG CTGTAGCAAA CTTAACAGCT ATAGCCTCCA
ATGCAAAACT 540

10

CCTTTTTTCTC CTATGTAGCT TTTGATCAAG AGAGATGCTT TTTAGTCTGC
TAAAAAAAAA 600

AAAAAAAAAA AAAAAAAAAA 620

15

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

20

(A) LENGTH: 1907 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

25

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CCGAATGTTT CCTGCAACAC AAAGATGACA ACCCCAGCCT GCCACCATTT
GAAAGGCCAG 60

30

AGGCTGAGGC CATGTGCACC TTCCATTTCA TTTCTGATGT TAAGAAATAT
TCTCTATCTG 120

35

GTTTGATAGC ACTTTGGGAC CATAGGGGAA AGAGTAGCAC CCACAGATAA
CAGGCTAAAA 180

AGCGTCTCTT GGTAAATGCT AGGAAGGAAA AAAAGGAGTT TGGCAGTGGG
GGCTATAGCT 240

5 GTTGAGCTTG CTACAGATCC ACATCCGAAG TGAATAGATC CTGGTACTGC
TGATCCCGTT 300

GTTGTTTCAGG TAGGCAAATC TTTCTCTCC CCGGATGGGA ATCGTGTTGT
TATACTCAGT 360

10 GTTGTCTGTC CACTTCCAAG GGTGCTCTTT GGCCTCTCAG CTTTCAAGTT
TCAATCCTGT 420

AGTGGAAGAACT CAGCTCCTCA GCTCTGAGAT GTGTGTCACA AAGGCTTCCC
TACCTATGCT 480

15 TAGTCCCACA GGCAGCCCGC AGGTAGAAGT GGGTAAAATT CTCCAAGGAA
AAAGGCACGG 540

AACCATCTCC CCTGAGTCTT GTGCTAAGCT TTACTGCTAC TATGGAGTGA
20 TCATGGTCCT 600

CACTGTAGCT GTAATTGCTC TTTCTGTTGC TTTGTCAGCA ACAAAGACAG
AACAGATCCC 660

25 AGTCAACAAG ACCTATGCTG CTTGCCCCGCA AACTGGATT GGAGTTGAAA
ATAAATGTTT 720

TTATTTTCT GAATACCCAA GTAAGTGGAC ATTCGCCCAG GCCTTCTGCA
TGCGCACAGA 780

30 GGCCCAACTA GCTCGGTTTG ACAACCAGGA TGAGCTGAAT TTCCTAATGA
GATACAAGGC 840

GAATTTTGAT TCCTGGATTG GCCTGCACAG AGAGTCGTCA GAGCACCCCTT
35 GGAAGTGGAC 900

AGACAACACT GAGTATAACA ACACGATTCC ATCCGGGGAG AGGAAAGATT
TGCCTACCTG 960

5 AACACAACG GGATCAGGGA ATTCCGGGAC ACCCGTCAGC ATTCCTGGAG
AAAATTCGGC 1020

ATTCATGAGA AAACGTCTTT TCTACTCCAG TGCTCTCAGT GACCAATGGC
TACTGAGTGC 1080

10 TGCTTCATCT GAACTGATCT GAATTGAGGC AAATGTAGGG TTGGCTTCCT
GCAGGAAGAC 1140

TGTTCAAAGC CAAGCTCTTT CCCTTCTAGG TGCCTGGGTC TAGTGCACAT
TAGTCTTGTT 1200

15 GGCAGCGTGT CTCCTCAGTC TGGCTATTGT GATCTTTCCC ATAGAAAGAG
TCAGGAACGA 1260

GGGGAAGGGA AAGATAGAGG CCTAAGGTGA AATTTTAAAA AACTCAATCT
20 GTTGGTTTGA 1320

TTTGTGGTTT CATGTTTGGG TGCAATTGTT CTTGAGACAA AAGTAGAACT
TTGAAATACT 1380

25 TTATTTAAAG AAACGAGTGC TCTGGCATT TAAATAAAC CTAATGTAAG
TCTATGAAGA 1440

GTTTCACTTA AATACATTTA TATAAAGAGC CAATGTTAAA AGTGTTATGG
ATAATAATTC 1500

30 TTCAAGGTGG TGGTTGTATT GGAACAAGTG TTCTTTCTGT CAGCTAGATT
CCTGGTATAA 1560

AATAATTTGA CTGCAGGGAA GTTGACAGAA AGCATTACTT CTGTATGCTA
35 CAACCCTTTA 1620

AAATTGTGCT CTGCCTCCAC CCATGTGGTG GTTTGAATGA AAATGTGGCC
ATAGTCTCAT 1680

5 ATTTGGATGT TTAATCACTA GGGAATGGAC CTGTTTGATA GGATTAGAAG
GATTGGAGGC 1740

GAGGCCTATT GGAGGAAGTG CCATACTGTG GATGGCCTTT GCCTAGTCTG
TCAACCCAG 1800

10 AGTTTTTCATG CCTGAGTGCT CCCTGCTGGA TAATGGAGTA ACCCTCTGAA
ACTGTAAGCA 1860

AGCTCCTGAT TAAATGCTTT CATTTCTAAA AAAAAAAAAA AAAAAAG 1907

15

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9349 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

TGCATTACAC ACACACACAC ACACACACAC ACACAAGGCC GGGCAGTGGT
GGTGCACACC 60

30 ATTAATCCCA GCACTGGGGA GGCAGAGACA GGCAGATTTC TGAGTTCAAG
GCCAGCCTGG 120

TCTACAGAGT GAGTTCCAGG ATATCCAGGG CTACACAGAG AAACCCTGTT
TCAAAAAAGT 180

35

TACTTTTTGT ACCTTGAAAT CTAAAATATG TCTCAACTCT GTTTGTCTTCT
TTTACAGTAT 240

AACATGCTCC CCCCCCCCCC CCGCCGCCGC AGTTTTTCAG TTCCAGATCT
AGGTAGGCAC 300

5 CCAATCTCTG GCAGCTTATC AAGTCAGCTG ATGTAAAAAT AATCCCACAA
CTCACAAAAT 360

ATAGAGGGAA GACAGCGGGG AAAAAGGGGC GGGCTCATTG CTTCAGCAAG
AAGATAGTGG 420

10 TGCATAGCCT CCCATGCCAG ATTGCTTGGA GACAGGAGAA AACTGTACG
TATTTAATGA 480

AATGCTAACT AAATAAAGT GGGGGAGGCT TCCTCAGGGG AGCTGGATCT
15 TGCTCCTGTT 540

AGCCTGCCAT AGTGGGTCTA TATAGACCAG CTGAGGCTGG GGTGGGGTGG
ATGGTGGGAG 600

20 CTCTGCTGTG GTCGGAAAGT ACCGATGCCA CTCTGGCTTT CTGGTATGGC
CAATGTTACT 660

TAAATACGTT TGGGAGGAGT GCAACCTTTT GAGTTTGTA ATAAAAGCAG
GTGCCCAGAT 720

25 TCCTGGAGGA TTGACTGGAG GACCTTGGGG GTGCTCTGGC ACACCCTGCC
ACCCAGCCCA 780

TACCTTAAGT GCCCCTCCTA CACACCTACC TACAACCTTC TTTTCAGGCT
30 CCCACAGTAC 840

TCCCCCTTTC CCAAACCTCC AAGCTTTTGG AATTTCTCTC TCTTCCAAG
GACACGGTAT 900

35 CAGGTAATAC TCTTTCTGGC CTAAATGAC TCTTGTTGCA CCAGGGAAGG
ATCAGTTTTT 960

TTCCAGTAGG GTGGGGGTGG GAGATTTATC CCATCTACAA ATCCATCTAC
AGTTTTAGTT 1020

CACTGGGTGC TGGGAATGAA CCAAGTCCTC TCTCTGCAAG AGCAGCAAGC
5 TCCCTTCCCT 1080

GTTGAGCCAT GACTTTACCC CCACTTTAAT ACTTTTGTTT AGGAATAAAA
TATCAATTTT 1140

10 CTTGAAAAGC AGAGTTCACA ATTGTTGTTA GATCAATGGC CTAGTGGCAG
CCTGAGGATA 1200

CCAGGCAAGC TCCTTCAGAG TGGACAGCCT AGCTGCTAAG ATGATTGGAA
ATACTGTTCT 1260

15 GGGAGGTGGG GGACAGGTCG AGGAAGAGGG AGACCTAACC ATGCCTCCCT
TCAACCCTAG 1320

GGCCCTACTC CATGCCATCC TGTGCACACC TAAAGTACCC TCCTCCACGG
20 CTATCCTGGT 1380

CCCTTAAACA GACCCTTAAT CAGAGTGTAG AACAGGGTCT TCTTGAGGCA
GAGTAGCAGG 1440

25 TATGATTGGC CTGCTGCCTT TGA CTGTGAG CTATAGCCAG GTTCCACCAA
GTTCCATACT 1500

CCTCACAGTA AGCCATAAGC GCCTGTTTGT GTTGGGAAAA CTTAGAAAAA
GTAAAGATTT 1560

30 TCTTTTGTTT TTGAGACTTT TCTATGGGTT AAAAATGGCG AGCCAGGGTC
CTACCAGCAG 1620

TGGGTCAGGG GGACATGAAA GGGACCTGAA TTTGGTGAAA AGGTACTGGA
35 TGTGGTGTCT 1680

CACAAGTGGG TCTTTTCTAG AAGCCCACCG CAGCTTTCTT TTTATGGTTT
TAACCTCCCT 1740

CTGGCTTAGT CCCCAAAGAG GAAAGGGCCG TGGAGGAAAT ACTAGTTGTG
5 TTCTTGAAAA 1800

AAAGCCATGT GCTTTTGTAG GGCAAGTAGT TTTAAAGGCA ACGCTTGAAG
GGGCCCTTAA 1860

10 AGAAAATCCG GGTAATGGCA GGAAGGTATT TTTATAAATT TTTGGTAAAG
GAAAATAACC 1920

TATATGGCCC CAACTGGGTT GAGTCCCAGC GTGGTCACCT TGGCTGGGGA
CAAGGGTGCT 1980
15

TCAGCTCCCA TGGATGTGGG AACTGGGCTT TGGGTGCCAG GGCTGGGGTG
GTGGAAGGTT 2040

TTGGGGTATG GCCCAAGTCG GAGGCTCCCA ACCAAACAGG CATCCAGCAT
20 CTTTCCAGTG 2100

GATGAGTGTG GAAAACCTGT GATACATACT CCCATATATA CTGGAATACT
ATGTACTAGT 2160

25 AAGATAGGAT GTCTTTTGTG ACAACATGGC TGGACCTGGG GTGACATGCT
GAGACAAATT 2220

AGTCAGGCAC TGAAAGGCCA ACATTGTTCA TCAGTTGTAG AGGGGTTTGT
TAGCTAAAAG 2280
30

CAGACAGGAG TTTACACTCT TTTCTTCGAT TTGGAAAGAT TTTTGAAATC
ACAGTGCAGA 2340

ACCTGAAATC ACAATGAAAC CAAACCACTC CTTTACAATC TGAAGGGGTT
35 TAGAAATCTC 2400

CCAAGACTTC CTTTCTATAG GGAGTGTGAG GAGGGCTGAG GAGGGCTCCC
AGCAGCACAT 2460

5 GGCTGAGAGG TGCTGGGGCT GGAAATGAGC ACAGGCGAAT TTATTATGCT
ATCATTTTAT 2520

ATTCTGTAGA ACTAGAAAGA ATTAAGGCTG GGAGTTCTGT GTGGATCCAA
AATGCAAAAG 2580

10 CTCAGTGCTT AAAGCCTTCT TTCTAATCCT AAGGCTCCTT TCCCTCCTTG
TTAATGTAAT 2640

AGAAGCTTTC TGGTATTTTA GGTGTGCGAA AATGCACAAA ATGCAAGGAT
TAAAGTCAGT 2700

15 GAAAACTCTG TAAAACTAT AATTAGCACT CAATAAAATT AATTCATTTG
GTATACATTT 2760

CTGTGAATTT TGAAAACATA TAATCAGGTG TTCTTCATTA AGATACATAG
20 GGGCTGGAGA 2820

CTTGGCTCAA CCACTGAGAG CATTTATTGC TCTTGCTGAG GACTGAGGTT
TCACTCCCAG 2880

25 CACACATATG GTGGCTCAAC ACCCACCCTT AATTCCAATT CCAGGGATCC
AATATATTTT 2940

CTAAATTCCT CTAACAGTAA TCATGCATGT AGTACACTAC ATACATACAT
ACATACATTA 3000

30 CATTCACACA TTCTTACATT TAGCTGACAA AGCACTCTTA AATGTAAAAT
AAATAAGACT 3060

AAAACAGTCA TTTTAAAAAT ATATACAGAC CCCCTACCCT ACCTGTTTCC
35 CCGTTGTCTG 3120

CTGCAGACAC TCTCACCCT CCTCCGCCAC AGCCATGAGT AGTCACCTTT
CCAGATGACT 3180

5 TAAAATGGGT CCATGAAGCA GAGAAGTCCC ACAAGAGTTC TTTCAGCTTG
TCACAGCAAT 3240

GCCTTCTGCT CATCACTCAC AGTGCAGTGC CAATCAGTAG TGTGTCAGAA
ACATGCACTG 3300

10 CTGGTGAGAT GCTGAGGGAT CATACCCATA GCATCGCCTA CACAGAATCA
TGCTCTGAGT 3360

15 TCAGAAATTT TTAAGAATCT CACCAGCAA TACTATGCAA AGAGGTGTG
AAAAGCTGTC 3420

AGGAACTTC TAGAGAAGTG ATAGGAGGAA GTGAATAGTG GCAGTTGGGG
GTCTCTTCAC 3480

20 AAAGGAACT GGGACTTCCT GTAGCTCTCT GACCTTTGCA TGAGCTTACT
TTCGGGTTAG 3540

TTTAGGGACA CTTTGGGGAA GAAGCCCTTG GGACATTGG CCTGTAAAG
TGGCATGAGA 3600

25 TAAGGCAAGC ACAGGCATGT GTTCCAAGTT GTTTCTTGTG TTGAGAGGTT
TACCTTGTC 3660

30 TCAGCTTGGG GATATTTTAA TGGTCACAAA TGTGTCATTT TCACAGGGAT
CCTTAAAGCT 3720

GCTGCAAATA TTCACATAAA GATGTCTTGC AACTTGAATT CCTTTCCAGC
ATGGGAATAT 3780

35 GTGGGTAGGA TGGGAGCATA TCACATTTTA CACTTACAAA CAGCTTTGTA
GAAGCTGTAA 3840

AATTTAGCCT TAAGAAGTTG TTAGTTCTAC CTCAACATGG ACATCCACAT
CAATGTATAA 3900

5 CCATCCTGTT ATGCAGACAG TGATTTTGCT CTTAAATCGA AGATGATTTT
GCCCAAGACA 3960

AGTTCACAAA CATTCCTTA CTTTTCTAAA AATCAAATGA CTTTATGATA
TTAAGTTTTG 4020

10 TGCTTGGGAT CTCTATGTCT ACAAATGGAC TGTAGAAATT TATGCCTATT
TATTTATTTA 4080

15 TTTATTTTTT TAGGAGACAG ATGGAAGGGT GTTTCAGTAG CACACACGGG
GAGTGATGCC 4140

ATCTTTTCCC TGTCTAAAGA CTGGTTCATC TCTGGTTAAG TGGTCTCTTG
ACCACCCACA 4200

20 TGTGTTTGAC CTCATTGTGG AGTCCTGTTT TCTGCTGTGT TGTTTCAGTG
TCTACTCTGA 4260

TGCTAGCACC AGGCTTTCAT TCCTGTTCCC ATGAGAACAT GAGACATCAG
GTCAGGCCTT 4320

25 GTGATCTTTC TGATTTTGAC CTCTTCATTC TCAGAATAAT TTTTGACTAT
TAATTTTTGA 4380

30 CTCTTTTTTAA TTTTCATATT ACTTCTCATA CAACTTGGTG CTATGATTTT
TTTTTTTCTG 4440

AAGGCAACTA CATCTCTGGA ATATGTTACA CATATATGTG TGTTTCAGAAA
TTGTTGACAT 4500

35 GAGCAATATG GAGTGTTCTA GTTCATTATG TGTTTAGCGC TGCCTTGATT
TCTTTCTTTA 4560

TTTCAAAAAT GTAACATGTA CGAGTGCTTC GCCTGCATAG ATATCTATGG
ATTGTGTGCA 4620

5 TTCCTAGTGC CCACCAAGGT TAGGAAAGTT CTCAGACTTC CTGAATATGG
ATTTACAGAG 4680

GCTTGTGAGC TCTTATATTG GTTCTAGATT TAACCCAGGT CCTCTGAAAG
ATCAACAAAT 4740

10 GTTCGAAACC ACTGAGCCAA CTTTCCTTTT TATTTCTTTA TATATTTACA
TG TAGTTTTT 4800

GTTATGCTGA CTATGAACAT CCTATTTTTA GATTGTGAAT TTTATGTTTT
TTTGGCATT 4860

15 CTGTCTAAGA TATTAATTTT CACTTGACAG GACAATACAA CTGATTTTAC
CATGCTGTCA 4920

20 CCCTGTCCTG CAGTTTTATA AACTCATTTT TTTTTTTTTT TTTACATCCA
ACGGTCTTTT 4980

GTAGATTTGT TTGGATTTTT ATGTAGATAG AACCTGTCA TCTGTGAAAA
GAAACACTTT 5040

25 CACCTGTTTC TGAGAAGCAT AAACCTCCTT TCGTTCTTTA AGAGACTCAT
TTTATGTATG 5100

TGGCTGTTTG CCTGCAGGTT TGTACATAAC ATGAATGCCC AGTGTGTACA
GAAGCCAGAA 5160

30 GAGGGCAATG GACCCCTTGG AACTGGAGGT GTGCAATGTT GTAAGCTACC
TTCAATTCAA 5220

35 GTCCTCTGGA AGAGCTGAAA GAGATCTTAA CAGCTGAGCC ATTCTCCAGA
CACCTGACCC 5280

TATTTCTTTG TCCTGGCGAG CACCTCCTGG GAAAAGTCTA CCTGGAGTAA
TGAGCAGACA 5340

5 TCTGACTCTT GCTCCTGATT GCTGGGAACA CATTCATAAT GGCACCATTG
AGAGTGCAGC 5400

TGACTGAAGT TGGACTTACT GCTTTGTTTT TAATGGATGA ATTTTGTAGG
GTTGAAGAAG 5460

10 TTCCTTTCAC TTCCATTTTC CACATATTTT TGTTGTTTAT TGAGATATTT
CTAATTTTTC 5520

CTCTTTTCTT ATTTTGTAAT ACATCTAATT ACATCAATTT ATTTTCTAGT
GTTTCTACAA 5580

15 CTCCTTCTAG CCAGGGCGCT TTTTATGGAG CCAAACCAG ATTTTGTGTG
TTTGCATGTC 5640

ACTGGGATCT CCACTCCGTC CATTTTTGCT CTTCCATTAT TCACCCTGAG
20 TTCAGTGATC 5700

AGAAGTCTCC CTGGCAGAAG TTCTGTTTCC ATCCTCTCTA GACTTCTTTC
TACCATGGAC 5760

25 ATCCTTTGTG GACCAGGGCC TTCTCTAAAA GGGTTGGCAG AAGCCTTTCA
GGAAGTATA 5820

GGCAATTGTC AAGTGGGTTT TGTGGTTATT TTATTTTATT TTATTTAAGA
AATTCTTGAA 5880

30 ATTCGCATTC TTATATTCAT ATTTTACAGA TAAAATTCTC CAAAGAAAAA
GTCTCAGAGC 5940

CATCTCCCCT GAGTCTTCTG CTAAGCTTTA CTGCTGCTAT GGAGTGATCA
35 TGGTCCTCAC 6000

TGTAGCTGTA GTTGCTCTTT CTGTTGCTTT GTCAGGTAAG TGACATACCC
TCCAAATTCT 6060

5 GTGACACTCT GTCCATATTC ACATTGCCAG TTATGCTTTC TAAGCACTGT
GATCCAGGCA 6120

CTGTGGCAAG GGCTCTAGAG GAAACACACT GGAAGGTCCT GTTCTCTGAG
AATTTAGGTT 6180

10 CCAACAGGAA GATGCAGTGA AGGAACACAG AGGCTTTGAT GGGGACATCC
CCGGGAAGAT 6240

GACATCCAGC AAGCTCTAGA CAGAGATGCA GGGGACATAG GTCCCCTTGG
GGGAACAATT 6300

15 CAAGGCAGAG AATAACAAGA GGGAATCTCC AAGTAGAAAC TTCAAAGGTG
AGGCCAGGAA 6360

20 GGTACAGTGC CTTTGACCAT GACCCATGAG TTTAGATACC AGGCTCAACT
CTATTTTGAA 6420

AGTATTAAAT GGAAAGTTCC TGAAGTAAGA AATTTATAGG ATTTTAGTAC
CACAATATTC 6480

25 AGAATAGTGC AATACAATCT TGCACTGTCC TCTTAAGTAT TTGAAGTCAT
CCTTTAGTGC 6540

AAGGTGTCTG CACCGTATAT ACGACCTACC CAAAATTCT CATAGAAATC
TCAATTATCA 6600

30 GGCTGGGTGT CAGTAGGTGT CCCTACAGAG TGCTTGCTGC TGTAGCAATC
CCCACTGTAG 6660

35 TCAATGGTCA TCCAAAGCTC AGAAAGTGAT GCTGTTATAG AAGTGCACTC
CCTGGGAGCC 6720

CTACTGACAG TGAGCACCTG AGAGAGAATG GGACACAGGC CCACGGTGGG
AGGCCTTTAG 6780

TTAAAGGCAC ATCTCGATCA GGAGAGGATT CCTACAGATC AGTTAGGAAA
5 GCTACCATCA 6840

GATTCACACC TCACAGCTGA GCTCAGGAGA GTGTGGCAAA ACGAGAGAAG
ACCTGCTTGC 6900

10 TATGATCCAT CATATTCTCT ACATTTTAGT AACAAAGACA GAACAGATCC
TAATCAACAA 6960

GACCTATGCT GCTTGCCCGA AAAACTGGAT TGGAGTTGGA AATAAATGTT
TTTATTTTTC 7020
15

TGAATACACA AGTAACTGGA CATTTGCCCA GACCTTCTGC ATGGCACAAG
AGGCCCAACT 7080

AGCTCGGTTT GACAACGAGA AGGAGCTGGT AAGCAATGGG CAGGGATTGG
20 TTTGTCTGTC 7140

TGTTCTGTTG AATATTATAT TGCCTTGAGA TAGAGAGTTA CAGATGAGGC
CCGAGGAAGG 7200

25 GATCCCACCC AAGCACATGG AGACATAGGG AATGTGAGTG TGTGCCATTT
GCTGATGCTT 7260

GACTTCTGAC TGGAGCCCTG AGATAGTCAA GAAACATTCT CTCATGAAGT
GCTCATAGTC 7320
30

AGCTGGAAGG TCAAATATGC CATTTTACTG GGATACCTGG TGACCATGAG
TGTTTTCCCA 7380

TATGCTGGCA TATGTTGGGT ACAGAAGGAG ACAACTGATA ATAAGTGCAG
35 TGGAAGGTTA 7440

ACCCAGAACT GTCCAAACCA CAGAGGAATG TGACCCTCAG TTACATCCTC
CTGTTATCTC 7500

5 TAGAGAAAGG TGTGGAGTGG AGAGACTCCA GGATCATCTG AAACAAATAG
ACACATGTAT 7560

TCTTGACTTT TTTGTGTTTT ATGACAGAAT TTCCTAATGA GATACAAGGC
AAATTTTGAT 7620

10 TCCTGGATTG GACTGCACAG AGAGTCGTCA GAGCACCCCTT GGAAGTGGAC
AGACAACACT 7680

15 GAGTATAACA ACATGTATGT TTTCACGATG TTTTTCCTTC TATTATGTTC
ATGTGTTGTG 7740

ATATGTGTGT GTCGTGGCTA TGAGAGATGG AAGTCAATGT CATGTGAAGC
CAACTGTACT 7800

20 GGGAAGAAAG AAAAAAAAAAT GAACCCTTGC CTGGAGGTGT GGCTCAGGGG
TAGAGAGTGT 7860

GTATAAATGC AATATCCAAT CCCCAGAAAG CTCTACACAC CCACAAATTT
AAATACTTCA 7920

25 GAGGTTTTCC TGTTTATTGA CCGTCATTTT CAAAACCTTT GCATCATGTC
ATTTTACTCA 7980

30 AAATATTTAC CATAATGATG GTGTCTGAGA GTAGCTATTG TTTGCTCTGG
CTCCAACCTA 8040

AACATTTCTG TTGTTGATAA ATGTCCTGTG AGGGATATAG ACAGAGCCTT
AGATGGGCAG 8100

35 TGGGGGCTCT GGAATCCCAG AAAGCCACTG CAGTATCTGC AAGCCTGAGA
TTCAGCTTTC 8160

CACTATTTGC ATGTCTGCAC CTG TTCAGGA AAGCAGAGAC TCTAAGTACA
TTTGGAACCT 8220

5 CCTCTAAAGT CTCGTCATCA CTGAGCACCC AAAACAGTCT TGGGTTTGAG
CTGTTTTACT 8280

GGGATGGTAA ATCACAGACT CAGTCACATC CATCACTGAA GCCCTTAGAG
CAATTTACTA 8340

10 AGTGGGCGTC CCCATATATA AAATGCCTAA AACAGAATTG AAAATCACCC
TTGGTGGGGT 8400

CACTCATGGC TGCAGTTCAT TTGAACATGG CAGCGAGCAC CAGCCCAATG
CCTTGTTACAC 8460

15 ACATTACAGG ATTCACCATG GACAAATGAC AAAGGAGTGG TGTTCAAATC
CTGAGAATAT 8520

GAGACAGTAG GTGTAAAACT AATGCAGGTG ATTCCTCAGG GACTTTTTGA
20 TTCATATTAC 8580

CAAAAATTAG TGGAGACTGG TGAGATTTCA TTGCAGGAGC AAATGCAGTT
CTGGGCTCTG 8640

25 TAGGCTTACT TTTTGGTTT CTTTTCAGGA TTCCCATCCA GGGAGTGGAA
ACATGTGCCT 8700

ACCTGAGCGG CAATGGGATC AGCAGTTCCA GGCATATAT ACCTCGGATA
TGGATCTGTA 8760

30 GCAAGCTTAA CAACTATAGC CTCCACTGCC CAACTCCTGT TCCTGTCTAG
CATTTACCAA 8820

GAGACTCTTC CTAGCCTGTT ATCTATGGGT GCTACTTTTT CCCCTATGGT
35 CCCACAGTGC 8880

TATCAAACGG GATTGAGAAT ATTTTTTAAC GTCGCAAATG AAAACCATCA
AGGCTGGAGA 8940

5 GATTGCTCCG TAGTTAAGAG ACTGACTGCT CTTCTGCATG TCCCGAGTTC
ACATCTGAGC 9000

AACCACATGG TGTCTTACAA ACATCTGTAA TGACATCTTA TGTCTCTTTC
TGTGGTGTGT 9060

10 GAAAACAGCT ACACTATACC TACATATGAT AAATAAGTAA ATCTTAAAAA
AGAAAAAGAA 9120

AACCACCTTA GAGAGGTGCA CACATGGAGG ATTACAAGAC CATAGATGAG
TTTTAAATAG 9180

15 ATGTCAGCAC TCATACCTTA AGCCTAAAGT ACAACTAATG TTAGGGAACC
CCACTTTTAT 9240

20 GATATTAAGG TTTTGTGCAG AGAATTCTTC TTTTGAATTT ATGAGACCAC
AAAAATGAGT 9300

CCCCCAACAT GGGTGTAACC TTTAATAATG AAAGCAGAAT GGCTGGGAT 9349

25 (2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 990 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GATAGTGGTG CAGAGCCTCC CATGCCAGAT TGCTTGGAGA CAGGAGAAAA
ACTGTTTGTA 60

CATAACATGA ATGCCCAGTG TGTACAGAAG CCAGAAGAGG GCAATGGACC
CCTTGGA ACT 120

5 GGAGATAAAA TTCTCCAAAG AAAAAGTCTC AGAGCCATCT CCCCTGAGTC
TTCTGCTAAG 180

CTTTACTGCT GCTATGGAGT GATCATGGTC CTCACTGTAG CTGTAGTTGC
TCTTTCTGTT 240

10 GCTTTGTCAG TAACAAAGAC AGAACAGATC CTAATCAACA AGACCTATGC
TGCTTGCCCCG 300

AAAACTGGA TTGGAGTTGG AAATAAATGT TTTTATTTTT CTGAATACAC
15 AAGTAACTGG 360

ACATTTGCCC AGACCTTCTG CATGGCACAA GAGGCCCAAC TAGCTCGGTT
TGACAACGAG 420

20 AAGGAGCTGA ATTTCCCTAAT GAGATACAAG GCAAATTTTG ATTCCTGGAT
TGGACTGCAC 480

AGAGAGTCGT CAGAGCACCC TTGGAAGTGG ACAGACAACA CTGAGTATAA
CAACATGATT 540

25 CCCATCCAGG GAGTGGAAAC ATGTGCCTAC CTGAGCGGCA ATGGGATCAG
CAGTTCCAGG 600

CACTATATAC CTCGGATATG GATCTGTAGC AAGCTTAACA ACTATAGCCT
30 CCACTGCCCA 660

ACTCCTGTTC CTGTCTAGCA TTTACCAAGA GACTCTTCCT AGCCTGTTAT
CTATGGGTGC 720

35 TACTTTTTCC CCTATGGTCC CACAGTGCTA TCAAACGGGA TTGAGAATAT
TTTTTAACGT 780

CGCAAATGAA AACCATCAAG GCTGGAGAGA TTGCTCCGTA GTTAAGAGAC
TGACTGCTCT 840

5 TCTGCATGTC CCGAGTTCAC ATCTGAGCAA CCACATGGTG TCTTACAAAC
ATCTGTAATG 900

ACATCTTATG TCCTCTTCTG TGGTGTGTGA AAACAGCTAC ACTATACCTA
CATATGATAA 960

10 ATAAGTAAAT CTTAAAAAAA AAAAAAAAAA 990

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

20 (iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TCCCATGCCA GATTGCTTG 19

25

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGGACCATAG GGGAAAAAGT AG 22

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 721 base pairs

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

TCCCATGCCA GATTGCTTGG AGACAGGAGA AAAACTGTTT GTACATAACA
TGAATGCCCA 60

15 GTGTGTACAG AAGCCAGAAG AGGGCAATGG ACCCCTTGA ACTGGAGGTA
AAATTGTCCA 120

AGGAAAATGT TTCAGAATCA TCTCCACTGT GTCTCCTGTT AAACCTTACT
GCTGCTATGG 180

20 AGTGATCATG GTCCTCACTG TAGCTGTAAT TGCTCTTTCT GTTGCTTTGT
CAACAAAAAA 240

GACAGAACAG ATCATAATCA ACAAGACCTA TGCTGCTTGC TCAAAAAACT
25 GGA CTGGAGT 300

TGGAAATAAA TGTTTTTATT TTTCTGGATA CCCACGTAAC TGGACATTTG
CCCAGGCCTT 360

30 CTGCATGGCA CAAGAGGCCA AACTAGCTCG GTTTGACAAC GAGGAGGAGC
TGATTTTCCT 420

AAAGAGATTC AAGGGGGATT TTGATTGCTG GATTGGCCTG CACAGAGAGT
CGTCAGAGCA 480

35 CCCTTGGAAG TGGACAAACA AACTGAGTA TAACAACATG AATCCCATCC
TAGGAGTGGG 540

AAGATATGCC TACCTGAGCA GCGATAGGAT CAGCAGTTTCG AGGAGCTATA
TAAATCGGAT 600

5 GTGGATCTGT AGCAAGCTCA ACAACTATAA CCTTCATTGC CAAACTCCTC
CTGTCTAGCA 660

CTTACCAAGA GACTCTTCTT AGCCTGTTAT CTATGGGTGC TACTTTTTTC
CCTATGGTCC 720
10 C 721

(2) INFORMATION FOR SEQ ID NO: 16:

15 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

25 TGGAAACTCA GTCCTCAGC TCTG 24

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 713 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

35 (iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

TGGAAACTCA GCTCCTCAGC TCTGAGATGT GTGTCACAAA GGCTTCCCTA
CCTATGCTTA 60

5 GTCCACAGG CAGCCCGCAG GAGGTAGAAG TGGGTAAAAT TCTCCAAGGA
AAAAGGCACG 120

GAACCATCTC CCCTGAGTCT TGTGCTAAGC TTTACTGCTA CTATGGAGTG
ATCATGGTCC 180

10

TCACTGTAGC TGTAATTGCT CTTTCTGTTG CTTTGTGAGC AACAAAGACA
GAACAGATCC 240

15 CAGTCAACAA GACCTATGCT GCTTGCCCGC AAAACTGGAT TGGAGTTGAA
AATAAATGTT 300

TTTATTTTTC TGAATACCCA AGTAACTGGA CATTCGCCCA GGCCTTCTGC
ATGGCACAAG 360

20 AGGCCCAACT AGCTCGGTTT GACAACCAGG ATGAGCTGAA TTTCCTAATG
AGATACAAGG 420

CGAATTTTGA TTCCTGGATT GGCCTGCACA GAGAGTCGTC AGAGCACCCCT
TGGAAGTGGA 480

25

CAGACAACAC TGAGTATAAC AACACGATTC CCATCCGGGG AGAGGAAAGA
TTTGCCTACC 540

30 TGAACAACAA CGGGATCAGC AGTACCAGGA TCTATTCACT TCGGATGTGG
ATCTGTAGCA 600

AGCTCAACAG CTATAGCCTC CACTGCCAAA CTCCTTTTTT TCCTTCCTAG
CATTTACCAA 660

35 GAGACGCTTT TTAGCCTGTT ATCTGTGGGT GCTACTTTTT CCCCTATGGT CCC
713

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

TTTGTCTAGCA ACAAAGACAG AACAG 25

15 (2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1229 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CGGGTGGGCG CGAGAGAGCC TAGAAGCCCA TGTAGCCGCG AATCCCGCAG
CCCCAGTACA 60

30 CCTCCCTCCG TGCCTCCCCG CCTTTTCTGC AGAGCTCCGC CCTGGAGTGA
AGGAGGAGCC 120

GTCACCTGGA GCTCCGAAAA AAGCAGAAGA AGGCGCTTTT TATTAGCCA
GTGTGACCCC 180

35 GCCAGGGCCT TCTCGGTTGG GTGAGCACTC TCTCTGACCA GGCCATGAAA
AGAAAAATCT 240

GTGCGATGCC TCCCCACATG TCACGGGACT CTGACTTGCC TTTGTCGTCA
GAGTTTGCAG 300

5 AACTTTGGGG GACCTGAGAG GGGAGTGCCC CCTGGACGGG CCACGGCTGT
CTGTGGCTTA 360

AGGGCTTTTG GAAGGGCGGA GAGAGGGAAA CGGCGTCCTA GTGGCCTGCT
TCAGGGCCAC 420

10 CCACGGGCCC TCCCCAACC TCTCTCTGAT CCAACTTGTT TTTCCAGCCT
AGTTGGAAAC 480

TTGTGGATGC TGTGACCTCA AGAAGACTTG GCATTTTATT TGGAAGATAG
ACATCTATTT 540

15 GCAACTGGTC CTGAGCCCCT ATTTTCCTCC CACCTTTCTT GGGGAAACTT
GTTTTTAAGG 600

GGTGCCACTG TTTTGTAAAC ATGTTGCTCC TAGCTCTTAG CATTGCTGGT
20 ACTGTTGTAA 660

ATGGAGAAAG AGTAATTCAC GCAGAGCCGG CTTTGCAGAT AAAACTCTGC
AAAGACAATG 720

25 TCTAGCACTT ATATCTCCAG TAACTCCTGT CAAGGTTTAT TGTGCTTGT
TCATCCATTG 780

CAGTCCTGAC TACAAGTGTG ATTGCACTTT CTATTGTTTT GTCAGAATTT
CCTGAAAAGA 840

30 TACAAAGGCC CTTCTGACCA TTGGATTGGC CTTAGAAGAG AATCATCCCA
TCGCATTTGG 900

AAATGGACAG ACAACATGGA ATATAATAAC ATGCTTGCTA TCAGAGGAAG
35 TGGAGAATGT 960

GCCTTCCTGA ATGACAATGG AGTCAACAGT GGCAGAATCT ACATGAACAG
AAAATGGATT 1020

5 TGTAGCAAGC CAAACAATTA TGTCTACAGT TGCCAGTTAT GTCCCCACTG
GGATACTACC 1080

TAGTAGAGCT GTGAGAAGAG GGCCACCATC CTCCAGACTC CAGAATGGTG
GAATCATCAG 1140

10 CAGCTTCCAC CATGCCCCTG GAAAAACTGC AAGTAACAGA CCTGCACATG
TATCCCCTAC 1200

ATCTAAAAAA AAAAAAAAAA AAAAAAAAAA 1229

15

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1336 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

CGGGACAATG TTATGTGGCT CAGAGGCCCT CCATGTATTC TTAACATTC
ACTCTCCTAT 60

30 CCTTCCAAGA ATAACACTAA TTTGACCTCT ACAATAATCA CTTTATCACT
CCAGTTTTCG 120

CTTTTTTCCT CAAAACAAT GCCTTTTAAG TCTATTTTAA TCGATAGATT
TCCTCTTAAT 180

35

ATCATTTAAA AATATTTCTT TACATTTTAA GACAGGAATC AGAATAATTT
GCTATGTTGA 240

ATTTCCAGTT ACTTGGATTT TGTTGATTTC ATTCCTGTGG TTTAGTTGAC
ATGAATCTCT 300

5 CCAATTGAAA GGGTAACTTG AATATGGTAG CTGGAAAGTT AAAATCAATT
CTTTTAACTT 360

TGGAAAATGA TTAAATTCTG GAGATAGAAT AGGTAAGGTT CATAAGATGA
CAGGGTCGTT 420

10 TGCATCCTTC TAGTGGAAAA GCGAAGGGAA TTAAATAAAA ATAACACTTT
GATGCTTAAT 480

15 GTTTCTGGCA GTATTATGTC TGTATTTAAT TGTTAAAATG TTTTTC AATA
ATTTTTTCCA 540

AGCGGGTTGT CTGCATTCAA AAGAGCATTC TATTAAAGCT ACCTTAATTT
GGCGCTTATT 600

20 TTTCTTAATC ATGTTTCTGA CAATCATAGT GTGTGGAATG GTTGCTGCTT
TAAGTGCAAT 660

AAGAGCTAAC TGCCATCAAG AGCCATCAGT ATGTCTTCAA GCTGCATGCC
CAGAAAGCTG 720

25 GATTGGTTTT CAAAGAAAGT GTTTCTATTT TTCTGATGAC ACCAAGAACT
GGACATCAAG 780

30 TCAGAGGTTT TGTGACTCAC AAGATGCTGA TCTTGCTCAG GTTGAAAGCT
TCCAGGAACT 840

GAATTTCTTG TTGAGATATA AAGGCCCATC TGATCACTGG ATTGGGCTGA
GCAGAGAACA 900

35 AGGCCAACCA TGGAAATGGA TAAATGGTAC TGAATGGACA AGACAGTTTC
CTATCCTGGG 960

AGCAGGAGAG TGTGCCTATT TGAATGACAA AGGTGCCAGT AGTGCCAGGC
ACTACACAGA 1020

5 GAGGAAGTGG ATTTGTTCCA AATCAGATAT ACATGTCTAG ATGTTACAGC
AAAGCCCCAA 1080

CTAATCTTTA GAAGCATATT GGAAGTATA ACTCCATTTT AAAATGAGCA
AAGAATTTAT 1140

10 TTCTTATACC AACAGGTATA TGAAAATATG CTCAATATCA CTAATAACTG
GGAAAATACA 1200

AATCAAAATC ATAGTAAAT ATTACCTGTT TTCATGGTGC TAATATTACC
15 TGTTCCTCCA 1260

CTGCTAATGA CATACCCGAG ACTGAGTAAT TTATAAATAA AAGAGATTTA
ATTGAAAAAA 1320

20 AAAAAAAAAA AAAAAA 1336

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 10221 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

30 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

GAATTCCTTC TTTTCTATT GTTTGAATA ATTCAGAAG GAATGGTACC
AGCTCCTCTT 60

35 CGTACCTCTG GTAGAATTCG GCAGTGCATT TGTCTGGACA TGGGCTTGTT
TTGGTTGGGT 120

AGGCTATTAA TTACTGCCTC AGTTTCAGAA CCTGTTATTG GTCTATTCAG
GAATCTGATT 180

5 TCTTCCTGGT TTAGTCTTGG GAGGGTGTAT GTGTCCAGGA ATTTATCCAT
TTCTTCCTTG 240

CCTGGGTATC ACCAGCAAAG GCTGAAGAAA AGCAAAGATT GCTGCCTGCT
CCTTCCTCTG 300

10 GAAGCTTCAT CCCAGAGGGG CACGCACCAG ATGCCAGCTG AGCTGTCCTG
TATGAGGTGC 360

CTATCAACCC CTGCTAGGAG TTGTCTCCCA GTCAGGAGGC ATGGGGGTCA
15 GGGACCCACT 420

TGAAAAGGCA GTCTTTCCCT CAGAAGAGCT CGAGCACTGT GCTGGGAGAT
CCTGCTCT 480

20 TTTCAGAGCT GGCTGGCAGG AATGTTTAAG TCTCCTGAAG CCGTGACCAC
AGCCACCCTT 540

TCCCCCAGGT GCTCTGTCCC AGGGAGATAA GAGTTTTATC TATAAGCCCC
TGACTGGGGC 600

25 TGCTGCCTTT CTTTCAGAGA TGCCCTGCCC AGAGAGGAGG AATCTAGAGA
GGCAGTCCGG 660

CTGCAGTGGC TTTGCTGCAC TGGCTTTGCT GCACTGTGGT GGGCTCCGCC
30 CAGTCCGAAC 720

TTCCCCCAGG GCTTTGTTTA CACTGTGAGG GGAAAATCAC CTACTCAAGC
CTCAGTAATG 780

35 GCGGATGCAC CTCCCCTCAC CAAGCTTGAG CATCTGGGGT CCACTTCAGA
CTGCTGTGCT 840

GGCAGCAAGA ATTTCCAGCC AGTGGGTCTT AGCTTGCTGG GCTCTGTGGG
GATTGGACCC 900

5 ACTGAGCAAG ACCACTTGGC TCCCTGGCTT CAGCCCCCTT TCCAGCAGAG
TGAATGATTC 960

TGTCTCAGTG GGTTCAGGC TCCACTGGGG TATGAAAAAA ACTCCTGCAG
TTATCTTGGT 1020

10 GACTGCCCAA ATCGCCACCC AGTTTTGTGC TTGAAACCCA GGGTTCTGGT
AGTGTTGGCA 1080

15 CTCCAGAGAA TCTCCTGGTC TGTGGGTGTC AAAAACCGTG GGAAAAGCGT
AGTATCTGGG 1140

CCAGATAGCA CCTCACAGCA CAGTCCCTCA CAACTTCCCT TGGCTAGGGG
AGGGAGTTCT 1200

20 CCCACCCCTT GTGCTTCCTG GGTGAAGCAG CGCCCCACCC TGCTTCTGCT
TGCCCTCTGT 1260

GGGCTGCACC CACTTGTGTA ACCAGTCCCA GTGAGATGAT CCTGGTACCT
CAGTTGGAAA 1320

25 TGCAGAAATC ACCTGCCTTC TGCATTGGTC TCACTGGGAA CTGCAGACCA
GAGCTGTTTC 1380

TAATCAGCCA TCTTGCCCTC TCTGGTCTGG TCGTTTTCTT TAAATTGGTT
GATACAGGAG 1440

30 CAGTGATAGC ACAACAAATA TGCACAGATT TGGGGAAAGT CATCCTGCAT
TATGGTCTGG 1500

35 TTCAAGAAAT TACATTTTAA TAGTTATAAT TTGGTATCAC CTTGTTTGTG
ATACCAAACC 1560

AGATAACAATA CACGTTTGCC TCATGTTATG ATTTGTTATT CAGATTACAC
CAGTTATTAT 1620

5 TCATAACTAA GAGTGATTTC TCATCTCACA AGAGCCAAAT CCAAGGATAA
TGGTGCCAAT 1680

TGATAGTAAT GATTCTATGA ATACCCAGCA TTCTGGTCTA TCATAGACAC
TTTCAGAACC 1740

10 ATTGAGTTGA AGGTAGAAGG TGGTTATATA ATAGAAGATG AACTGGTAGC
TACTAGGGGC 1800

15 TCAGTGACAA CTATCTGGAG AGACATTCAT TCATCTCGAT CCCACATGAA
GAGAGCATTT 1860

CTCCTGATTA TATAAGAAGT GGGTCAGAAA AGCCTGTCCA GTGAAGTATT
GCTGCCTTCA 1920

20 AAGTGTAGAA AACCTCACTA AATCTCCTTA GTGGAAGGAA GTTCACTGTA
CAACAACCTTA 1980

TTTCATATTT ATGATAGTAT TTAGACATAT ACAAGGCTTT TTCACATCAA
GAAACCTTAT 2040

25 TCACATAAGG CATCTCTATC CTGCCCTTCA TTTTACCAAG TCATCTGGAG
CAGCAATCGC 2100

30 CAACCTTGTT GGCATGAGGG ACCAGTTTTG TGAAAGACAA CGTTTTTCATG
GACTGGGGTC 2160

AAGGAATGGT TTGGGGATAA TTTAAGTGCA TTAATTTTAT TGTGCCCTTT
ATTTCCATTA 2220

35 TTATTACATT GTGTAATAAT ATATAATAAA ATAATTATAC AACTCACCAT
AATGTAGAAT 2280

CAGTGGGAAC CCTGAGCTAG TTTTCTGAA AGTAGATGGT ACCATCTGTG
AGTGATGGGA 2340

5 GACAGTGACA GTTCATCAGG TATTAGATTC TCACAAGGAG CCCACAACCT
AGATTCCTCA 2400

CATGAGAAGT TCCCAATAGG GTTTGCCCTC CTATGAGAAT CTAATGCCAC
TGCTGATCTG 2460

10 ACAGGAGGTG GAGCTCATGA GGTAATGTGA GTGATGGGGA GTGGCTGTAA
ATACAGATGA 2520

AGCTTCACTT ACTCATTCGC TGCTTACCTC CTGCTGTGCA GCCTGCTTCC
TGACTCATCC 2580

15 ATGGACCAGT ACTGATCCAT GGCCTAGGGG TTGGGGACCC CTAATCTAGA
GCACTTGGAG 2640

20 AACTATCTGT TCTCCAAAGC TGATCAAATG CTATCATTA TGTATCTAAT
ATTTTAAGAA 2700

AGGGTAACAC TGTTGAGAGC CAAATAGATA CATGGCCCAG AGCAAGCTTA
AGTTACTAAT 2760

25 AACTCCTTTT TCAGCTCACC CCCTGCTGAA GGCATGAGTT TGAATCTCAG
TTTTGCCATT 2820

TGCTGTGTAA TGTATGCAAT TATATTTAGC ATCATATTTT CCACTTGAAA
AATGAAAATA 2880

30 ATACATTTAA TACTTAACAG GAGTGTCAGA AAGTATATTA GCACTTGGTA
ATTTATACAA 2940

TACAATATAA AAGTAAGAAA TTTTATTTT ATTTATTTT ATTTATTTT
35 CAGCAATAAG 3000

AGCTAACTGC CATCAAGAGC CATCAGTATG TCTTCAAGCT GCATGCCCAG
AAAGCTGGAT 3060

5 TGGTTTTCAA AGAAAGTGTT TCTATTTTTC TGATGACACC AAGAACTGGA
CATCAAGTCA 3120

GAGGTTTTGT GACTCACAAG ATGCTGATCT TGCTCAGGTT GAAAGCTTCC
AGGAACTGGT 3180

10 AAGAAAATAG TTCTGGCCAG AATCAAAGAT TCAGCCCTAC AAGGATATGT
TTTCCTGTGA 3240

AATTATCTAA GAGGTAGGTT TAGACATCTG CTTTACATT GATTTTTTTT
TTTTTTTTTT 3300

15 TTTTTTGCAT AACGAAAGAG TAACCTAGCA TGTATTATAT TTTACAGTGA
ACCATCTAAA 3360

20 ATTACCTTAA TATTCGTGGC AGGAACAGGC CCAGAGGGCA AGCAAGCCAG
AGCCTTCTTT 3420

GACTTGTGAG CCAGAATTGT GCAAATAAGG ATTAGAAAAG TATTGGTAGA
AACCCAGTTT 3480

25 TAAGTTTGTA TGAAGTTAGC AACATTGTTT CAAAATAAAT CAAACAAGGC
CAAGAGCAGT 3540

GGCACATGCC TGTAATCCCA GCACTTTGGG AGGCCAAGGC GGGTGTATCA
CTTGAGGTCA 3600

30 GGAGTTTGAG ATCAGCCTGG CCAACATGGT GAAACCCCAT CTCAACTAAA
AAATACAAAA 3660

ATTAGCTGGG CATGGTGGCA TACGCCTGTA GTTCCAGCTA CTCAGGAGGC
35 TGAGGCAGCA 3720

GAATTGCTTG AACCTGGGAG GTGGAGGCCT ACAGTTAGCT GAAATCATGC
TACTGTACTC 3780

5 CAGCCTAACA GAGTGAGACT CTATCTCAA AAAATAATAA AATAAAAACA
ATAAGTCAAG 3840

CAAGAATGAT GTCATAGAGG TTGGTAGACT AAAAAGCTAC AGAAATCTGT
TCCTCCACTG 3900

10 AGAAAACTAT TGAAGTGTCA AAAACTGTCT GAAGTAACTA TTTTGAATT
CTCGAGTCTA 3960

15 GTTAAACACT GGAAGCATCA AGGGAAGAGT TTGATAAAGA GGATGATAAA
TTTTGGTTAA 4020

TGTTGGTGAA TTTCAGCCTT TCCACTCAAT AATAACTATT TTCCATACCC
CATTATTGCA 4080

20 GGGATCCATG GGAAGTGTCT CCCATGTTCT TGTAATGAAT TCCTGCAGCC
AGGGTGAACA 4140

ATAAGCACCT TTTTGTCCAA ATGTCAGGGT TATTGCTGAT TTCTGCCTTT
GAATGCTGAG 4200

25 GGGCAGACAC AGAAGTGGGC TATCATTGCA TCAGTCCTCA TCAGCTGAAG
TGGCTTCCCA 4260

30 AGGATTTAAA TAAATAGTAT GTGTTTTTCC TCCCTTTAGG AAGCAGTCAT
TTAAGACAAT 4320

TTTTATTAGA TAACTGGCTG ACAGCAGAGA TAACAGAACA GAGATTTCOA
TGACCATGCA 4380

35 CAACAGAGAA TAAAAATAGT TGGGAAAAAA TCATGACCAA ATGACTCTGA
GCCACAACAA 4440

CCAAGATTTG ACAATCCCTG AAGAGCAAAA TAATTAAGTT ACCAGAGTTA
CCACAACATA 4500

5 GTATTCATAA TGTCCAGTTC TCAAAAAAAAA ATTACAAAAC ATGCAAAGAA
AAGTATGGTT 4560

CATTACACAGG AAGAAAAAGT AATCTGACAG AAACATATCCC TGAAGAGGCT
CAGATATTAA 4620

10 AAATATGAGT CAAAAATGTT AAATCAGCTG TCTTAAGTAT AACCAATGAG
TTAAAGGAAA 4680

15 CTAGACAAAA AGCTAAAGGA AACCGAAAAC ATAATAAATG AACAAAATTA
GAATATCAAT 4740

ATAAAGGTAG AAATTGTAAA AAAGAACCAA GCAAAAATTC CAGAGCTGAA
AAGTACAATG 4800

20 ACTGAAATTT AAAAATAATT TTAAAACTC AATGAAGAAG TTCAACAGCA
GATTTGAGAA 4860

GTAAGAGATC AGAAAACTTG AAAATAAGAT AATTGAAACA ATCCAGACTA
AGAAAAACAA 4920

25 AGAAAAAGAA TGAAGATAAA TAAATTCTAA GGAACCTGTA GGACATCAGC
AAACATACTA 4980

ACATATGTAC TGTAGAAATC CAGGAAAGAG AAGAGAAAGA GAAGCAGAGA
AATACACTTA 5040

30 AAGAAATAAT GAACAAAAC TTCCAAAATC TGAGGAAATA CATAAATATA
TACATCCAAG 5100

35 AGGCTCAATG AACTCCAAAA GGGTAACTT AAAGAGATCT ACATTGAGAC
AAAATATAGT 5160

CAAGTTGACA AAATCCACAG AGAGAATTTT GAAAGCAGCC AGAATGAAGC
AACTCATCAT 5220

5 TTACATAAGA CCCTGAATAA AATTAATAGC TGATTTTCTC TGAGAAACCA
TGGAGATCAG 5280

AAGGTAGTGG AATGGCATAT TTAAATGTCT GAAAGAAAAA ATAAAACTGC
CAACCATGAA 5340

10 TTCTATGTAT AGCAAAGTTG TCCTTCAAGA ATGAAGGAAA AAGTAACACA
TTTTCAGATA 5400

15 ACCAATAATT AAGGGATTTT ATTACCAGTA GACATGTGCT ACAGAAAATG
CTAAAGGAAA 5460

CCTTTTAGGC TGAAGTGAAG GTACACTAGA CAGCAATTCA GAGCCTCCAA
AATAAAGAAT 5520

20 ATTCATAAAA GTAACAATAG AGGTAAATAT AAAACCCAGA ATTACTACAT
GTGTCATATA 5580

GTTTATAACT TCTCCTATTT ATAGCTTCT ATATTTATAT TTATCTATAA
CTTCATAGGC 5640

25 AAATGAATAA AAATTATAAA TATGATAGTG GTCATATAAT GTATAAAGAT
GCAATCTGTG 5700

30 ACAGTCTTAT GAAGCAGGGA TGAAGACATA TAGGATCAAA ATGTTTGCAT
AGTTATTGAA 5760

GCTATGTTGA TATTATGAAA TTATATTGTT ACAAGTTTAA GATGCTAATT
ATAATTCTCA 5820

35 AGGTAACCAC TAATAAAATT ACCAAAATTA TGCAGAAAAG GAAAAAAGAA
AAACAATACA 5880

CTATAAAAAA CCAATTAAAT ACAAAAAAAG TCAGTAACAG ACAACTTGAG
AAACAAAGAC 5940

5 ATATAAGATA TAGAGAAAAC AAATGATTAA ATGGCAAAAG TAAATCTTGT
TTTAGTAATC 6000

ACATTAAATA GAAAAGGATG AAGCCATCCT ATTAAAGGGC TGAGACTGAC
AAGTTGGCTA 6060

10 AAAACTAAAA TAAATTAAAA AGAAAAACAA GACTCATCTA CATGCTGTCT
ATAAGAGACT 6120

15 TGCCTTAGAT ATAAGGACAC AAAGAAGTTG AAAGTAAAAG GACTGAAAAA
GATATTCCAT 6180

ACAAACAGTA GTAACCAAGA TAGTGCCGAG TGGCTATATT TTTGTCAAAC
AAAATAAACT 6240

20 AAAGTAAAAT TTACAAGAGA AAAAGAAGGG CATTATGCAT TGACAAAAAT
TTTGACATAG 6300

CCAAATAATT ATGTTATAAA ATATATGTAC TTAATAATAC AGCCTCAAAA
TATATGAAGC 6360

25 AATAATTGCT ATAATTTAAG GGAGAAAAGA ACAGTTCTAT GAAAAGTTAG
AGAATGAAAT 6420

30 ATTCCACTTT CAACATGAGA TTAAACAACT AGACATAAGA TCAATAAGGA
AATAGAAAAT 6480

TTGAACAACA CTATAAACCA ATTATCCCTA ACAGGCATAT ACAGAAGAAT
CTACCCAACA 6540

35 AGAGCAGAAT ATTAATTCTT CTCAAATGCA CATGGAACAT TCTTAAACCA
TATGTTAGGC 6600

CACAAAACAA GTGTTAGTAA GTGTGAAAAT TTGAAGTCAT AAAAAGTATC
TTTTGCAATT 6660

5 ACAATGGAAT GAAGCTAGAA ATCAATAACT AGAAAAACCA GAAAAGTCAC
GCATATGTAG 6720

AAATTTAAAA ACCCGCTCTT CAACAGCCAT TGGTCAAAGA AGAAATCACA
AGGGACATTA 6780

10 GAAAATACCT TGAGACAAAT GAAGTAAAAA TACAAATAGC ACGTTTATGG
TATACACTGA 6840

ACATAGTTCT AAGAGGGAAA TTTATAGCTG TGAGCAGTTA ACTAAAAAAG
AAGAAAGATC 6900

15 TCAAATCCAT AGCCTAACTG TACACTGTAA GGAAGTAAAA AAAGTAAAC
AAAAATAGAA 6960

20 GTCATCTTTA TGATTTGAAA GAGTAAAAGA TTTACCTAAT AAGTCCCTAA
ATTTACTAAT 7020

AATAAGAAA ATTGTTTATA TATTTAATTG CGTTAAAATT CAGAACTTGT
AATCATAAAA 7080

25 AGGACAGTAC ACATTGACAA GGAAACACAG CAAAGGAAAC CAGCCTATGC
TGCTGCTGTT 7140

30 GTGAGGATAA TTTGGTACAC TTACATTAGT TTGGTGTCTT TTCTTTCTCT
TTCTTTCTTT 7200

CTTTCTTTCT CTTTCTTTTCG TTCGTTTCGT CGTTCGTTTC TTTTGTGAGAC
AGAATCTCAC 7260

35 TCTATTGCCC AGGCTGGAGT GCAGTGGCGT GATCTTGGCT CACTACAAC
TTTGTCTCCC 7320

AGGTTCAAAT GATTCTCATG CCTCAGCCTC CCAAATAGCT GGGATTACAG
GTGCATGCCA 7380

5 TCACGCCCAG CTAATTTTTG TATTTTTTTT AATAGAGAGG GGGCTTCATC
ATGTTGGCCA 7440

AGCCTAGTCT CAAACTCTTG GCCTCAGGTG ATCCGCCTGC CTCGGCCTCC
CAAAGTACTG 7500

10 GGATTACAGG TGCTTGGCCT GGTGGTGTCA TTTCTTAAAG TTGACAAAAA
GCATATCCTG 7560

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TACATTCCAA 7620

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AGAGTCATAC 7680

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TCAGTTTTAA 7740

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ATTACTAAAC 7800

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GCAGCAACAT 7860

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TTCTGAAAGA 7920

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AGAGAACAAG 7980

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CTAAAAATCT 8040

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TCTAGTTACA 8100

5 TGCTTTAAAA AATTCTCATT TTAAGGTTAG TCATGAAAGA AGATGGTGCC
AACTTGTATG 8160

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AGGTAGACTG 8220

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TTTAAGCAAA 8280

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GCACTTGTCC 8340

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GAAAGATTAT 8400

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CTTCAGATTA 8520

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CAATATTGGA 8640

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TGAAATGAGT 8700

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TCTGTTACCC 8940

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TGGCTCAAGT 9000

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CCTTGCTTGG 9060

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GCCTGGGCTG 9120

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20 GTTGAATTA 9180

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ATATTATTAA 9240

25 CTAACCAGTT TTTGGAAACT GCTCATCACT TAAAGAAATG TAAAATATTA
TATGATTAAG 9300

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CCAATGAGCA 9360

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CCATCTAAAC 9420

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35 AGGAATAAAA 9480

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GCAAAATATT 9540

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GGCTTTGGAT 9600

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ACTTTGCAGT 9660

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35 AGTAATTTAT 10200

AAATAAAAGA GATTTAATTG A 10221

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GAGTGTGTC TGTCCACTTC C 21

15

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

TTTCCAACCTC CAATCCAGTT T 21

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GAGGAGCTGA GTTTCCACTA C 21

5

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

10

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

15

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

GGT AGG GAA GCC TTT GTG AC-3'.

20

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acid

(B) TYPE: amino acid

25

(C) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

30 H-Cys-Met-Arg-Thr-Glu-Ala-Gln-Leu-Ala-Arg-Phe-Asp-Asn-Gln-
Asp-Glu-Leu-Asn-Phe-OH

(2) INFORMATION FOR SEQ ID NO: 27:

35

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
5 (iv) ANTI-SENSE: NO
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GCCACGCGTT TGTCAGCAAC AAAGACAGAA CAG 33

10
(2) INFORMATION FOR SEQ ID NO: 28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
15 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: YES
20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

GCCACGCGTG GGACCATAGG GGAAAAAGTA G 31

25 (2) INFORMATION FOR SEQ ID NO: 29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 660 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
30 (D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

ACAATGGTTC TTGCCAGCTC TACCACCAGC ATCCACACCA TGCTGCTCCT

GCTCCTGATG 60

CTCTTCCACC TGGGACTCCA AGCTTCAATC TCGGCGCGCC AGGACTACAA
GGACGACGAT 120

5 GACAAGACGC GTTTGTCAGC AACAAAGACA GAACAGATCC CAGTCAACAA
GACCTATGCT 180

GCTTGCCCGC AAAACTGGAT TGGAGTTGAA AATAAATGTT TTTATTTTTC
10 TGAATACCCA 240

AGTAACTGGA CATTCGCCCCA GGCCTTCTGC ATGGCACAAG AGGCCCAACT
AGCTCGGTTT 300

15 GACAACCAGG ATGAGCTGAA TTCCTAATG AGATACAAGG CGAATTTTGA
TTCCTGGATT 360

GGCCTGCACA GAGAGTCGTC AGAGCACCTT TGGAAGTGGA CAGACAACAC
TGAGTATAAC 420

20 AACACGATTC CCATCCGGGG AGAGGAAAGA TTTGCCTACC TGAACAACAA
CGGGATCAGC 480

AGTACCAGGA TCTATTCACT TCGGATGTGG ATCTGTAGCA AGCTCAACAG
25 CTATAGCCTC 540

CACTGCCAAA CTCCTTTTTT TCCTTCCTAG CATTTACCAA GAGACGCTTT
TTAGCCTGTT 600

30 ATCTGTGGGT GCTACTTTTT CCCCTATGGT CCC
660

35

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

10

GCCACGCGTT CAGTAAAAAA GACAGCCAAG 30

(2) INFORMATION FOR SEQ ID NO: 31:

15 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

25 GCCCAGCGTA ACTACAGGCA CTGTGAGG 28

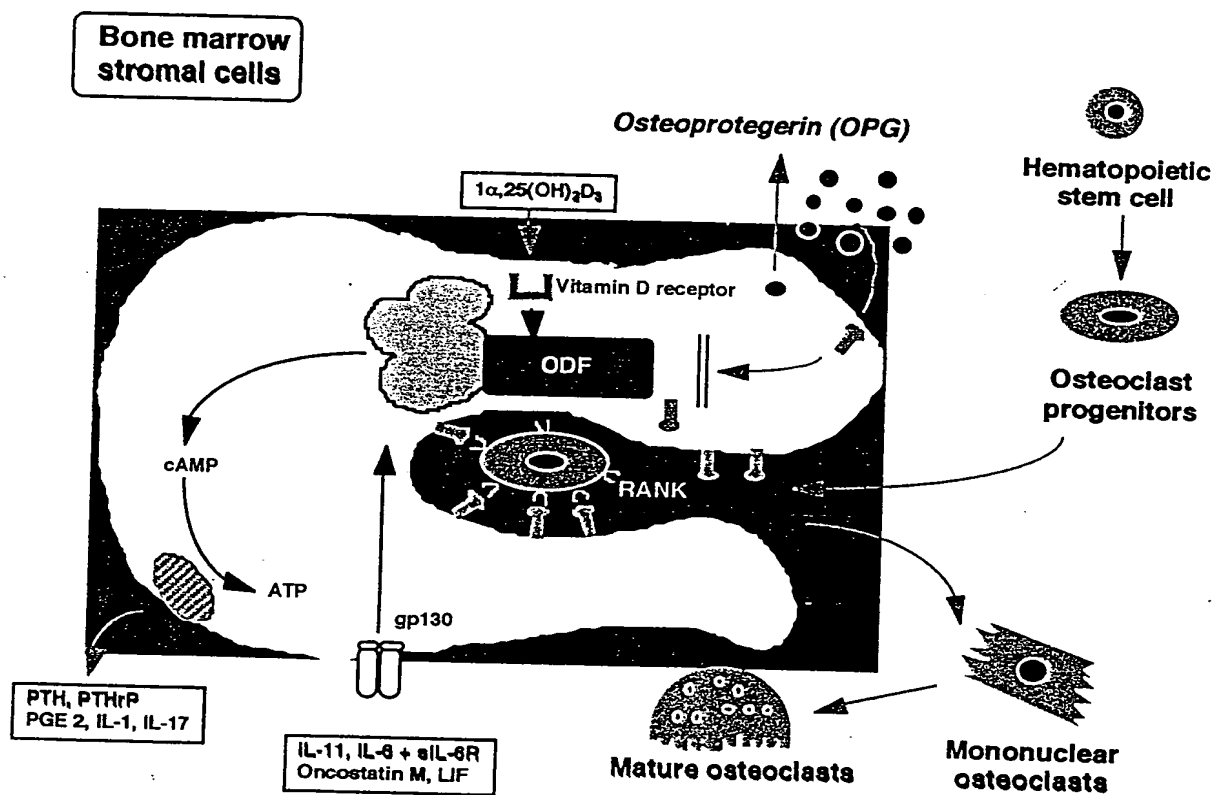


FIGURE 1

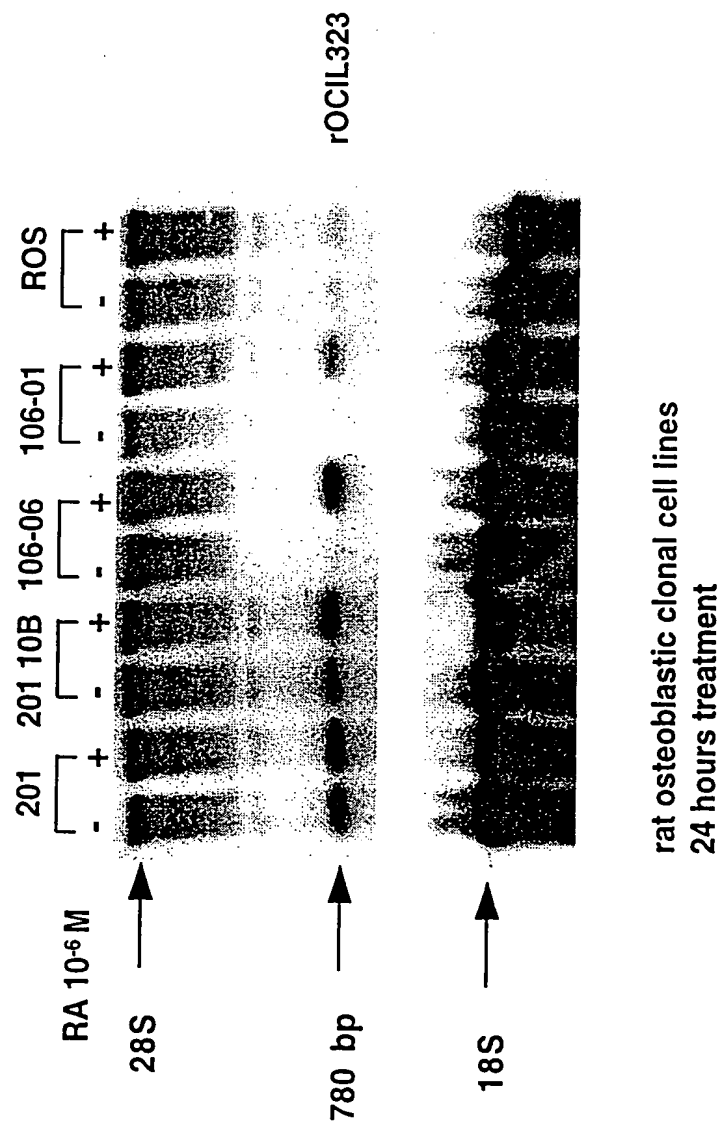


Figure 2

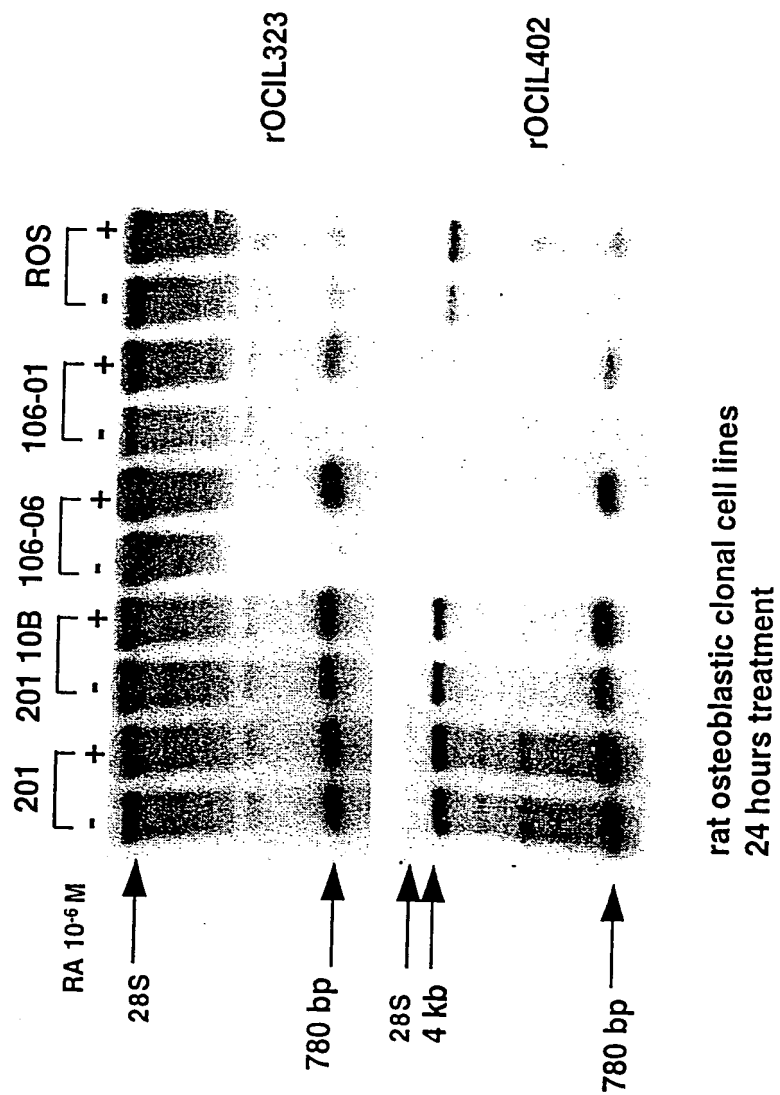
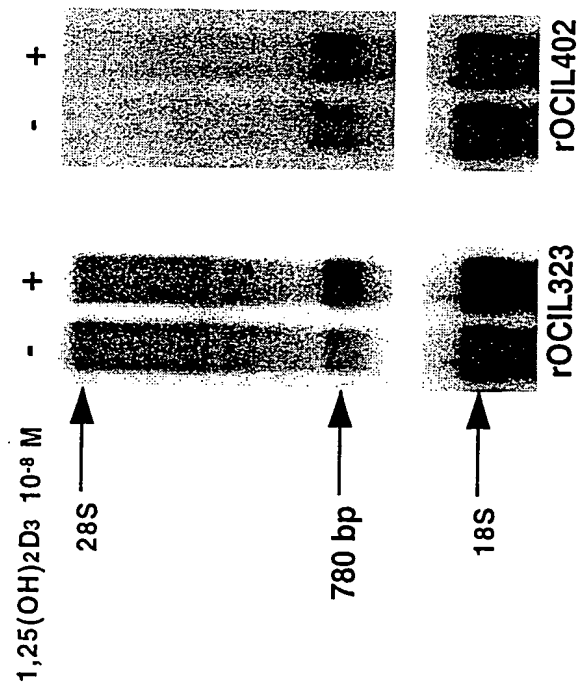


Figure 3



UMR 106-06 cells

Figure 4

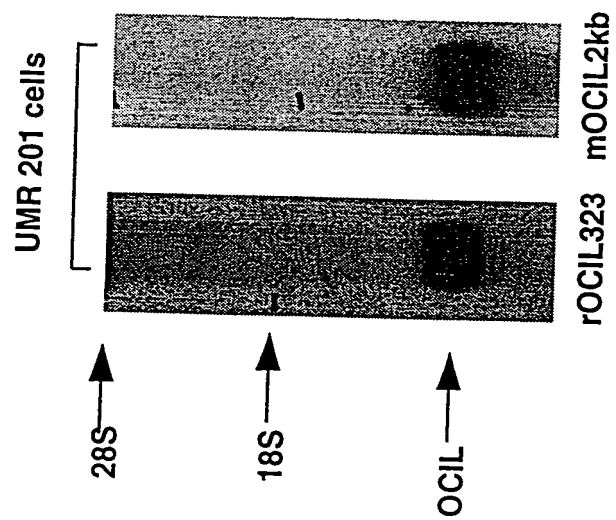


FIGURE 5

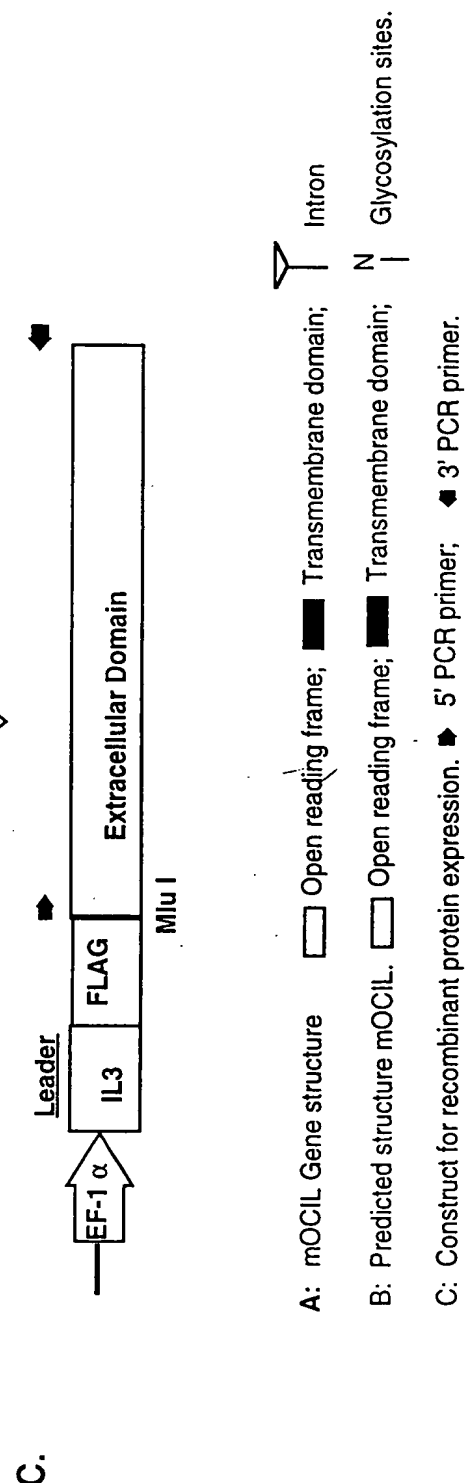
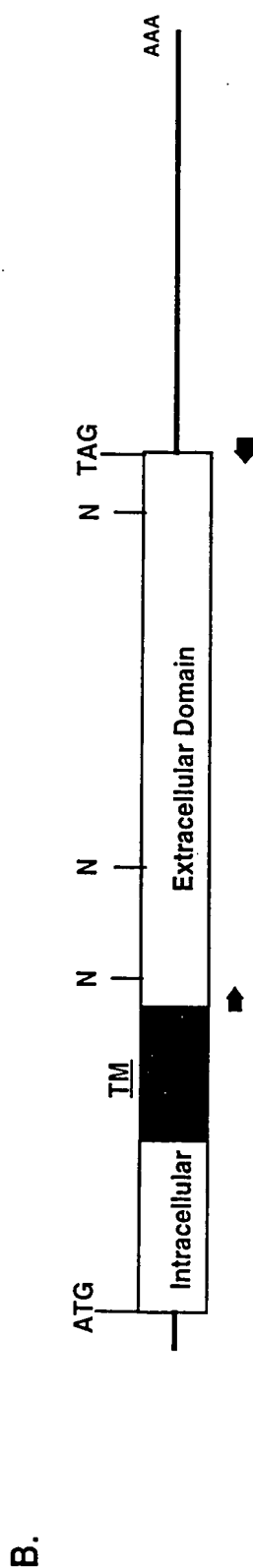
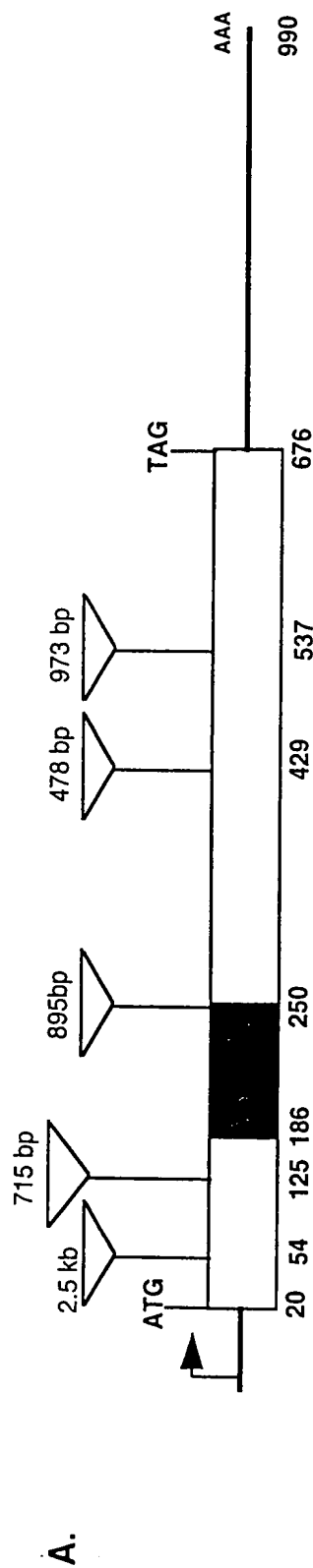


FIGURE 6

CrystalW Formatted Alignments

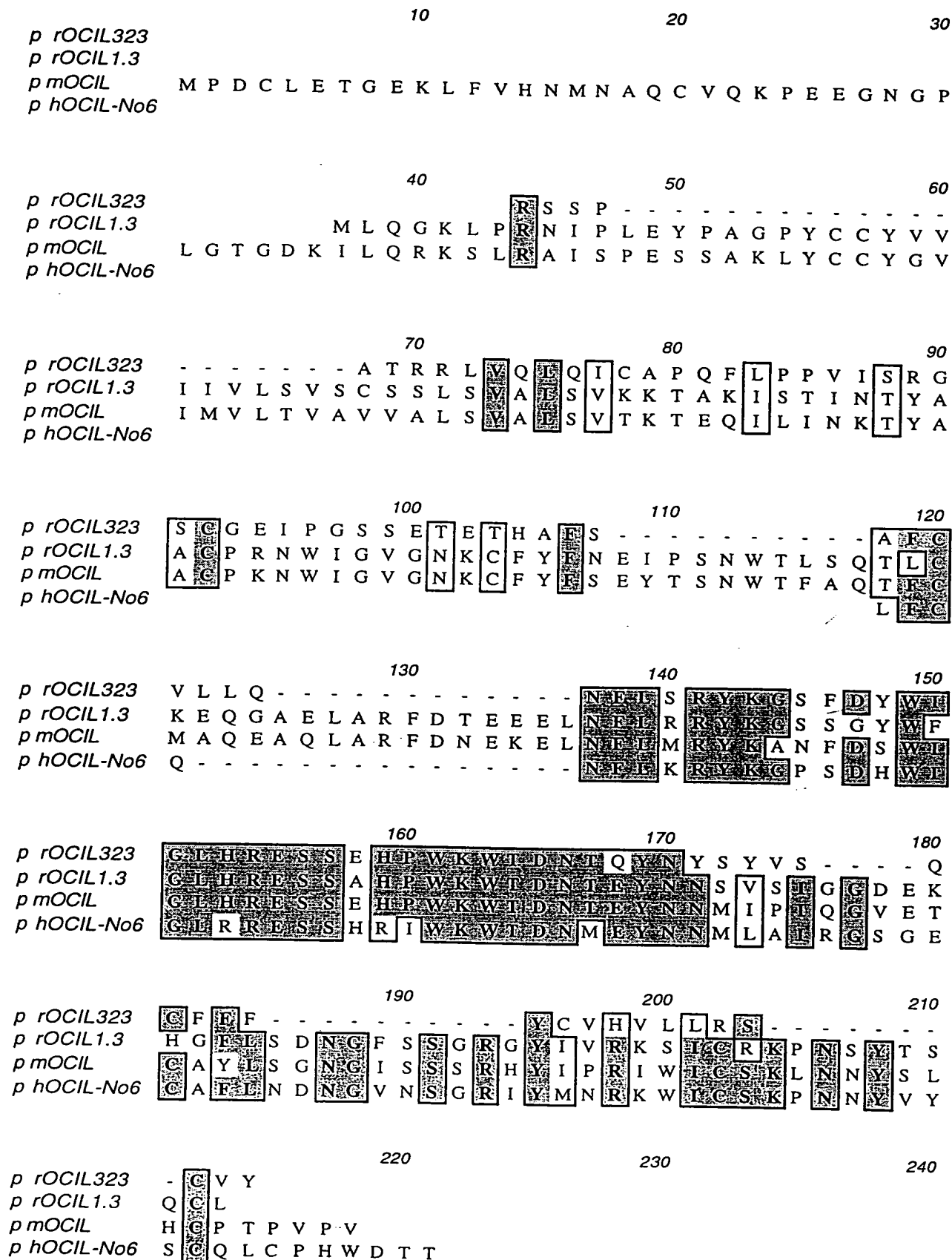


FIGURE 7

ClustalW Formatted Alignments

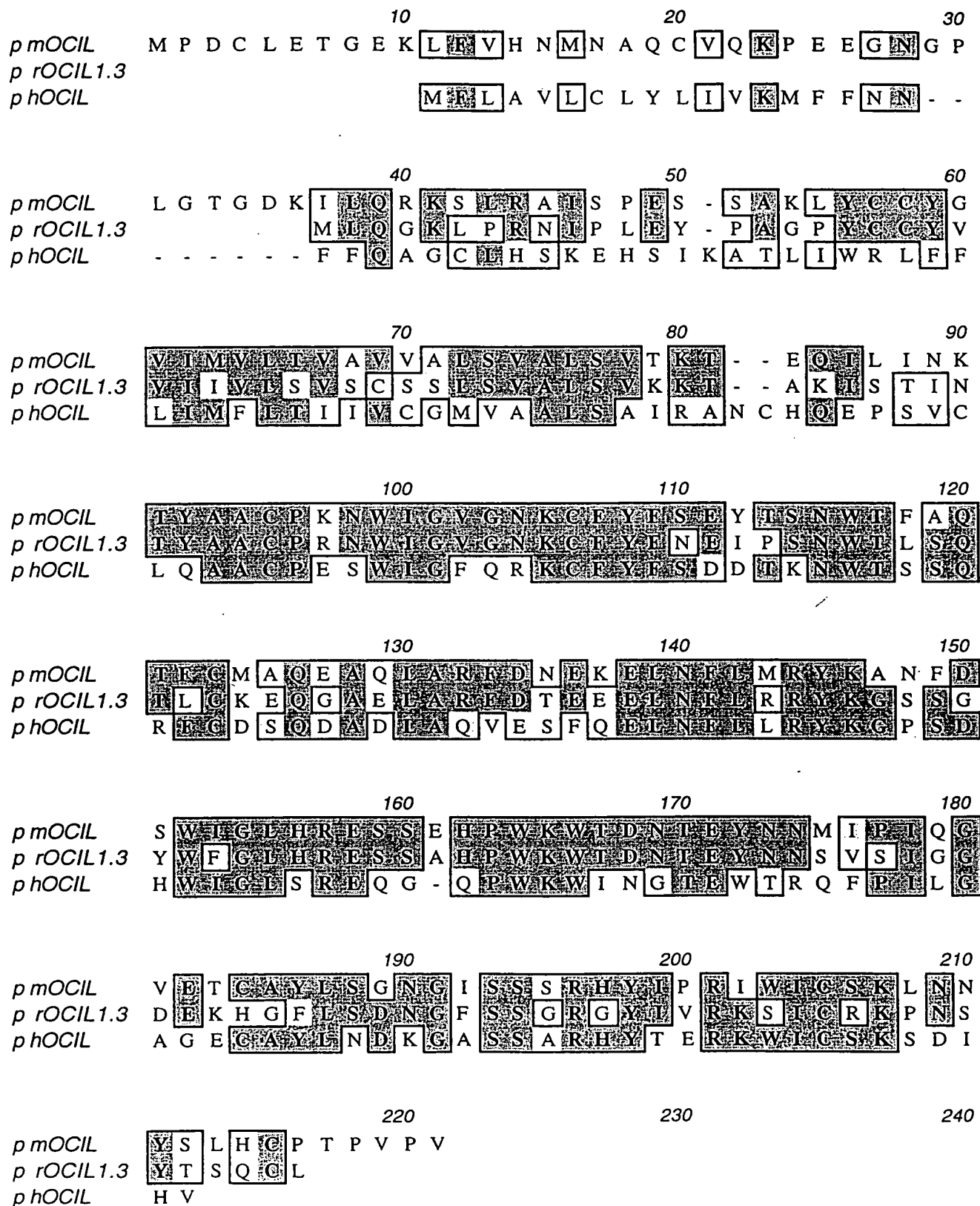
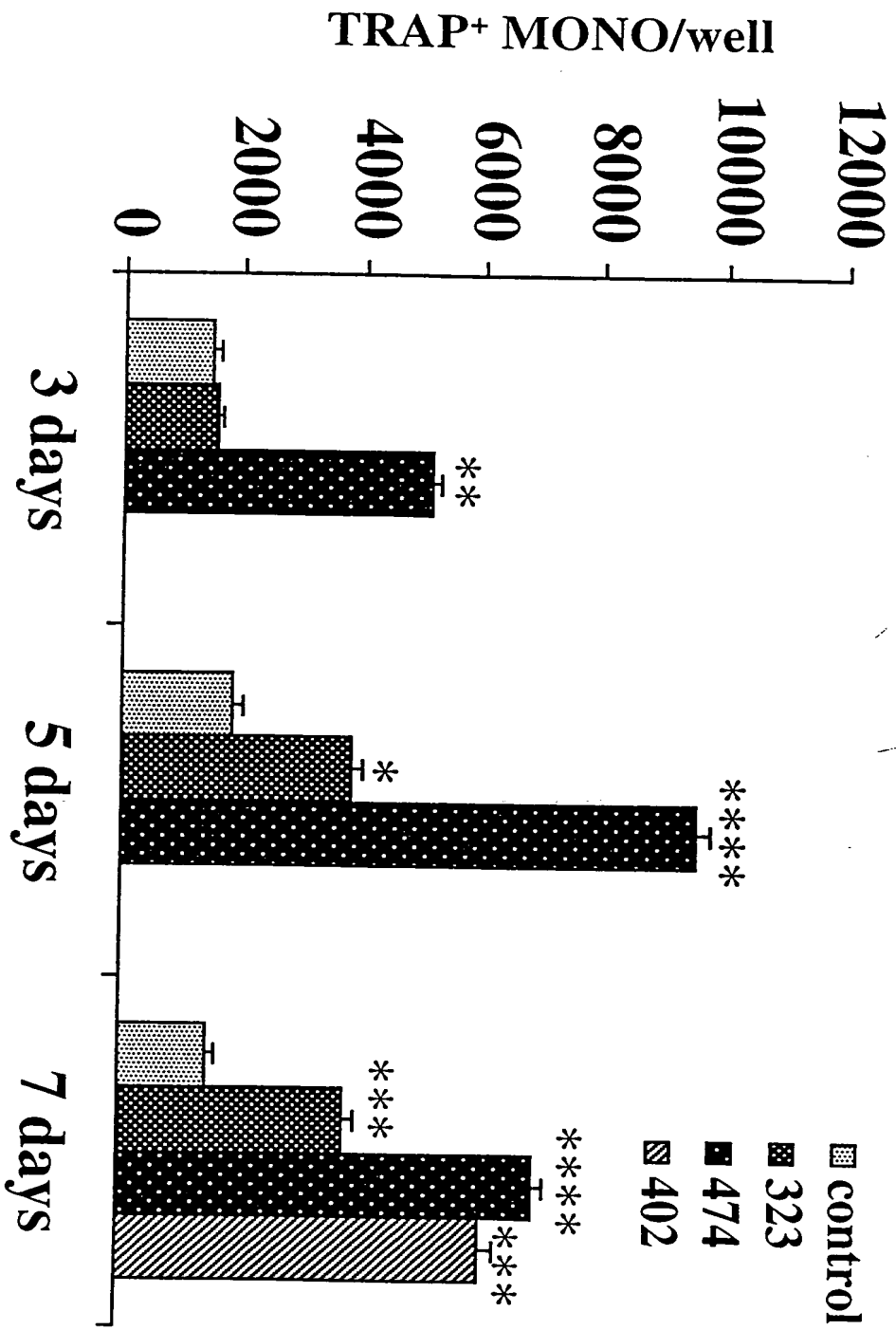


FIGURE 8

OB + BM CO-CULTURE



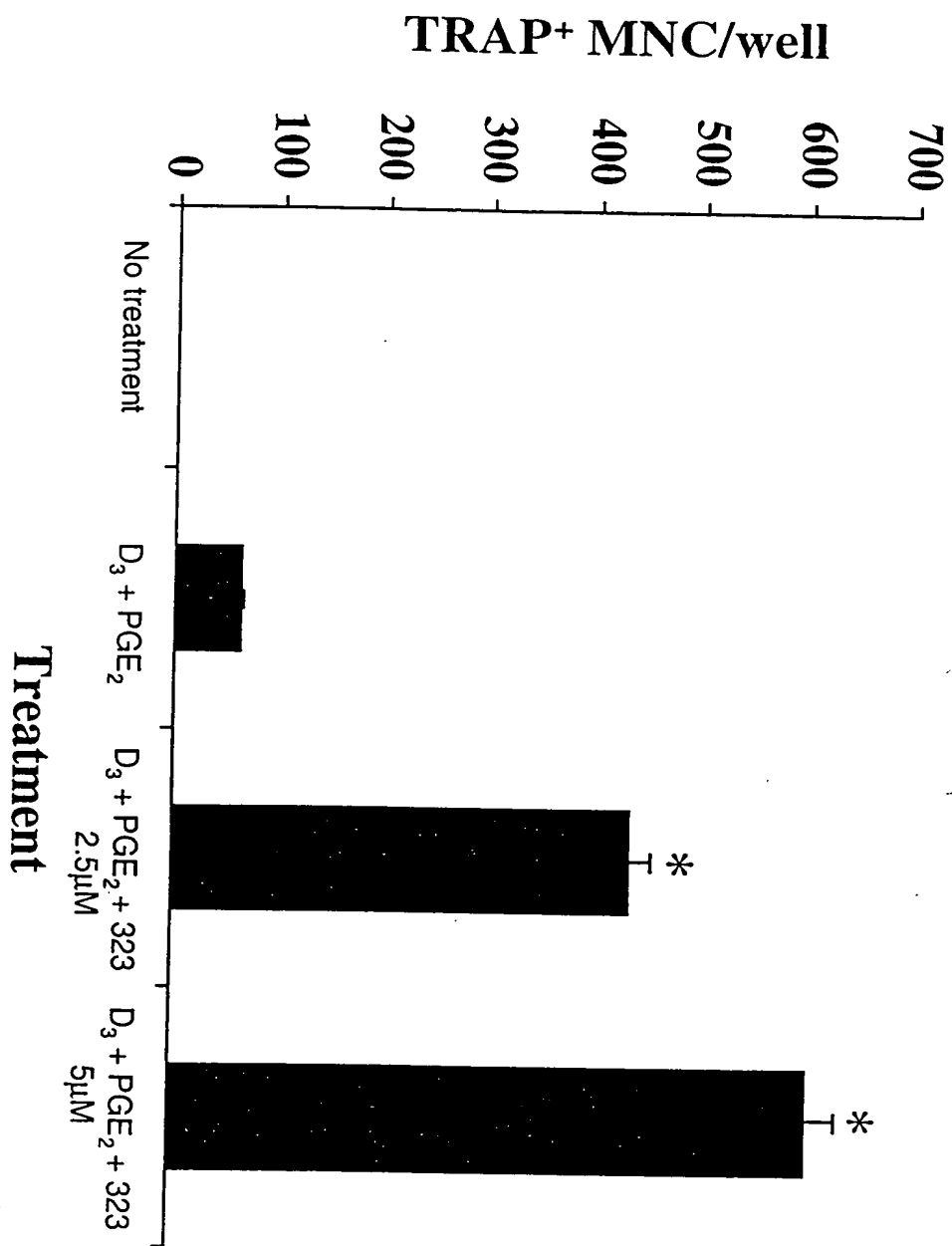
TRAP: tartrate-resistant acid phosphatase

MONO: mononucleate osteoclast precursors

*p < 0.025 vs control; **p < 0.005 vs control; ***p < 0.001 vs control; ****p < 0.0001 vs control

FIGURE 9a

OB + BM CO-CULTURE



TRAP: tartrate-resistant acid phosphatase

MNC: multinucleate osteoclasts

*p < 0.0001 vs D₃ + PGE₂ treated

FIGURE 9b

OB + BM CO-CULTURE

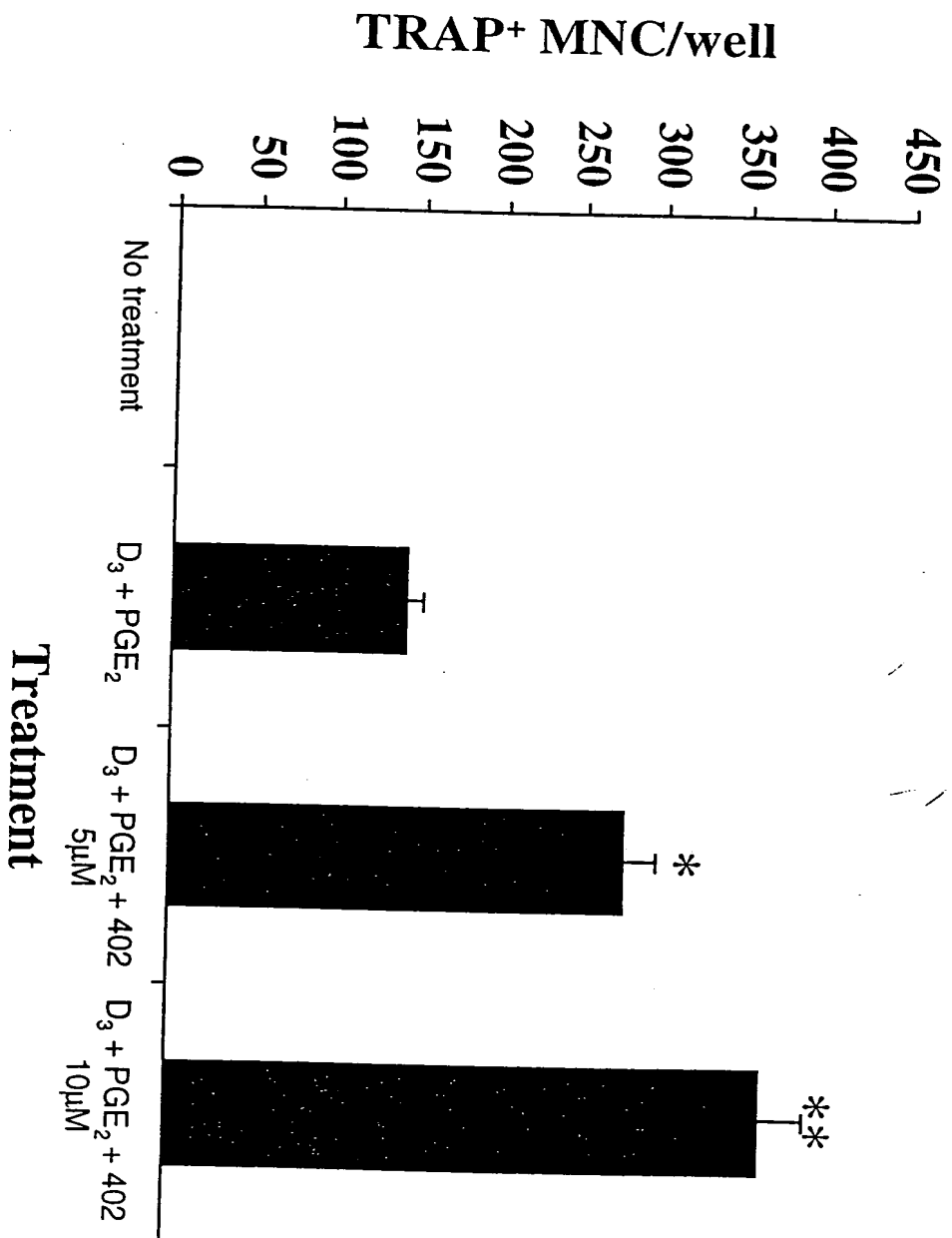
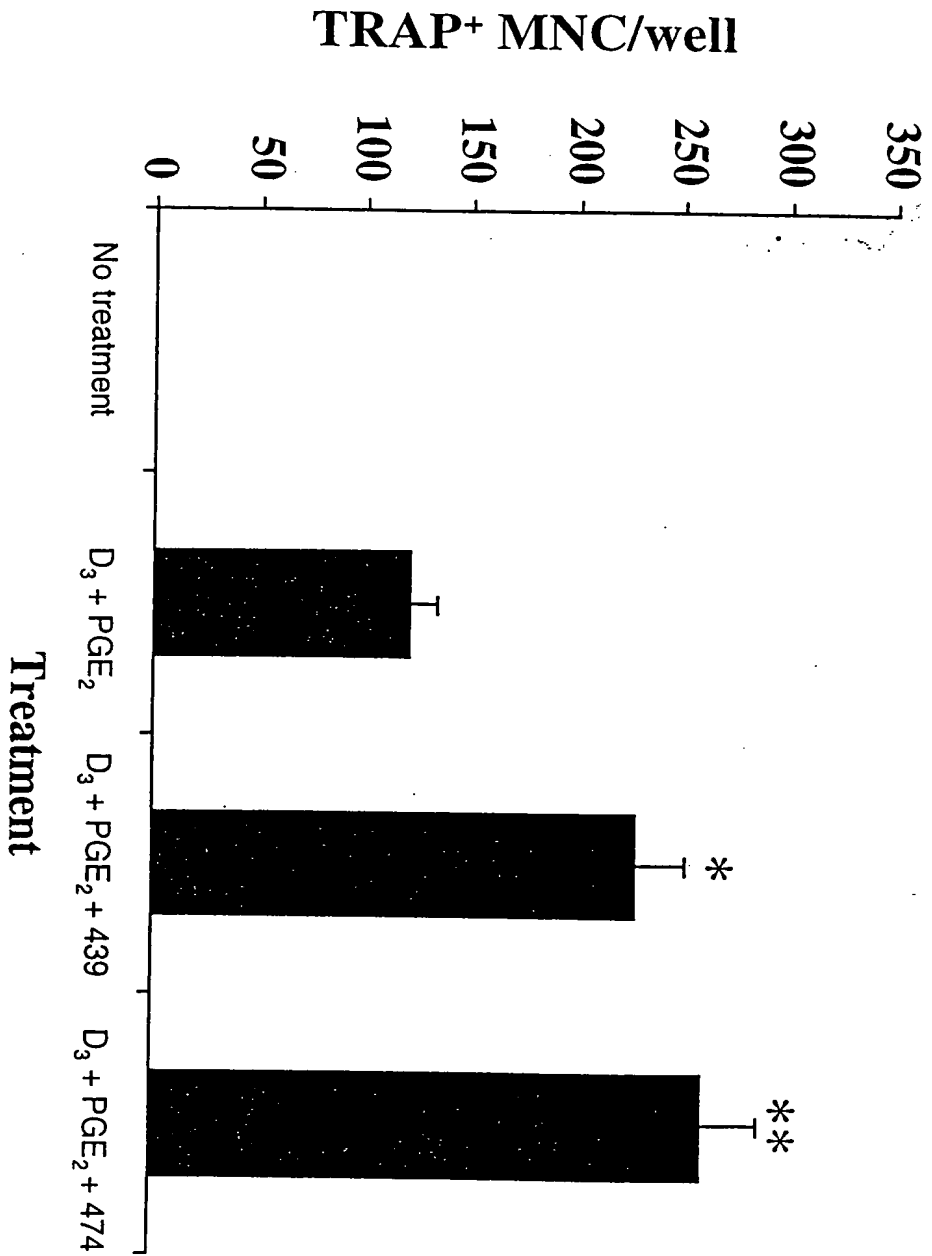


FIGURE 9c

TRAP: tartrate-resistant acid phosphatase
MNC: multinucleate osteoclasts

*p < 0.01 vs D₃ + PGE₂ treated; **p < 0.0005 vs D₃ + PGE₂ treated

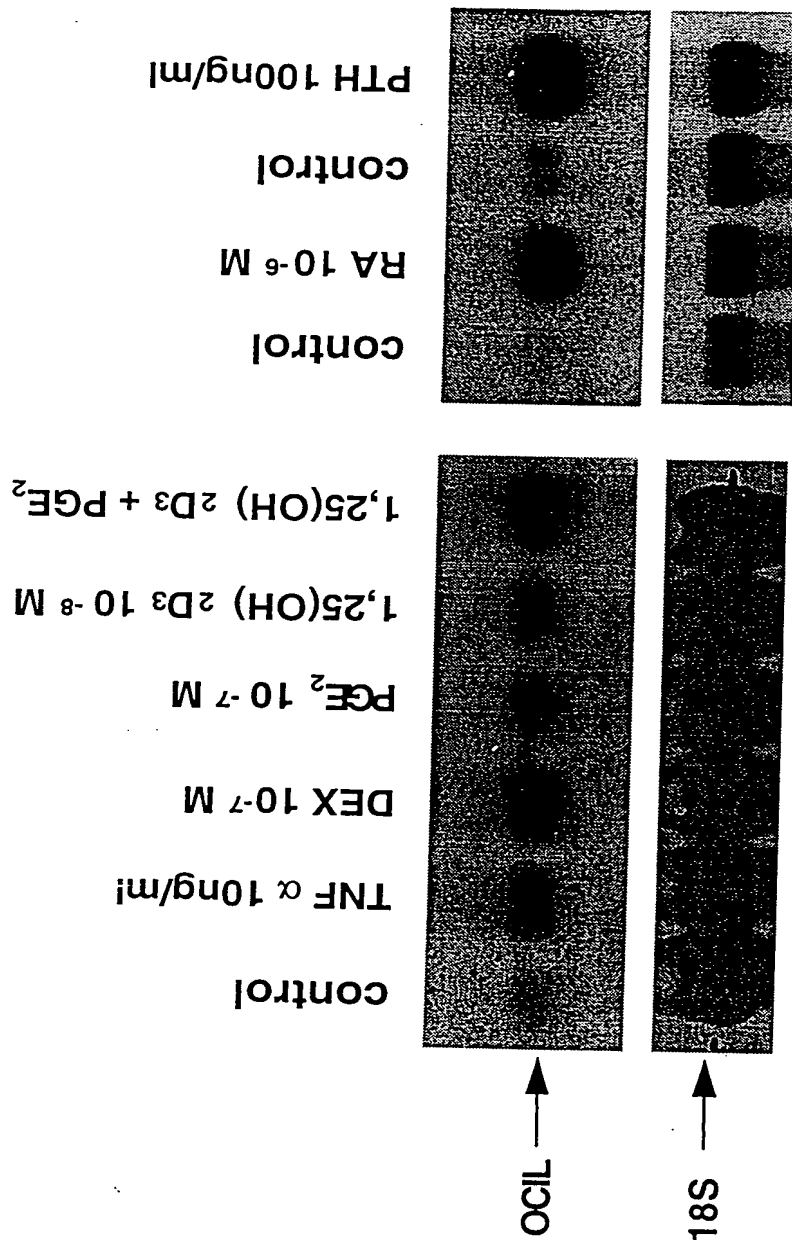
OB + BM CO-CULTURE



TRAP: tartrate-resistant acid phosphatase
MNC: multinucleate osteoclasts

*p < 0.025 vs D₃ + PGE₂ treated; **p < 0.005 vs D₃ + PGE₂ treated

FIGURE 9d



UMR 106 parental cells 24 hours treatment

FIGURE 10

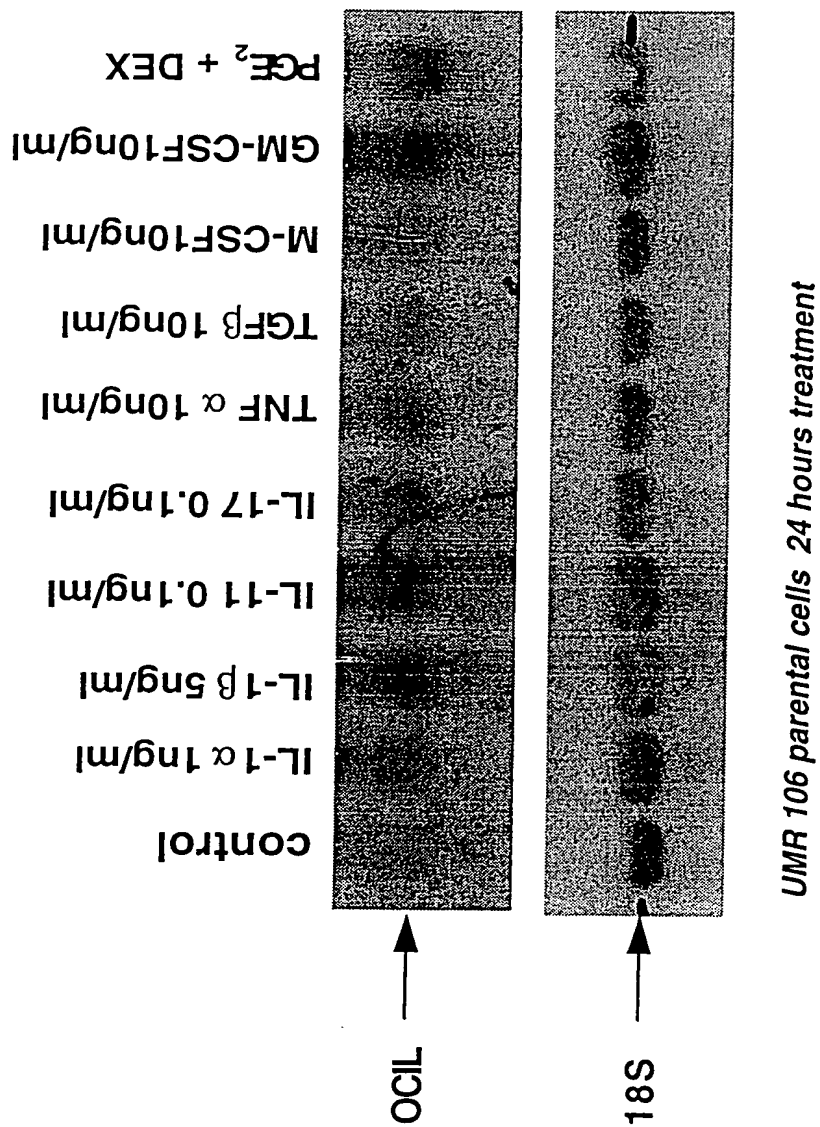


FIGURE 10 (cont.)

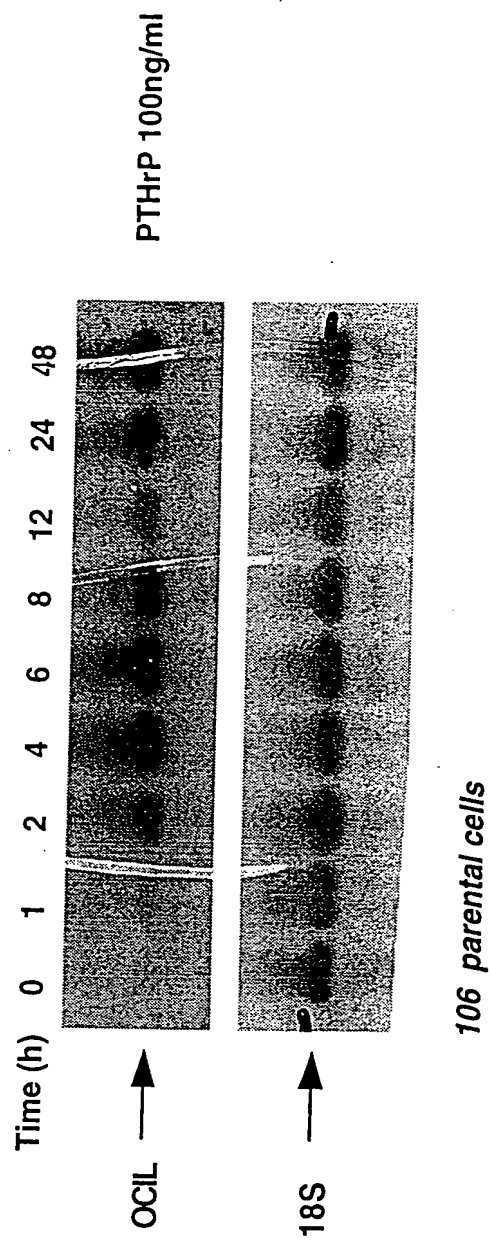


FIGURE 11A

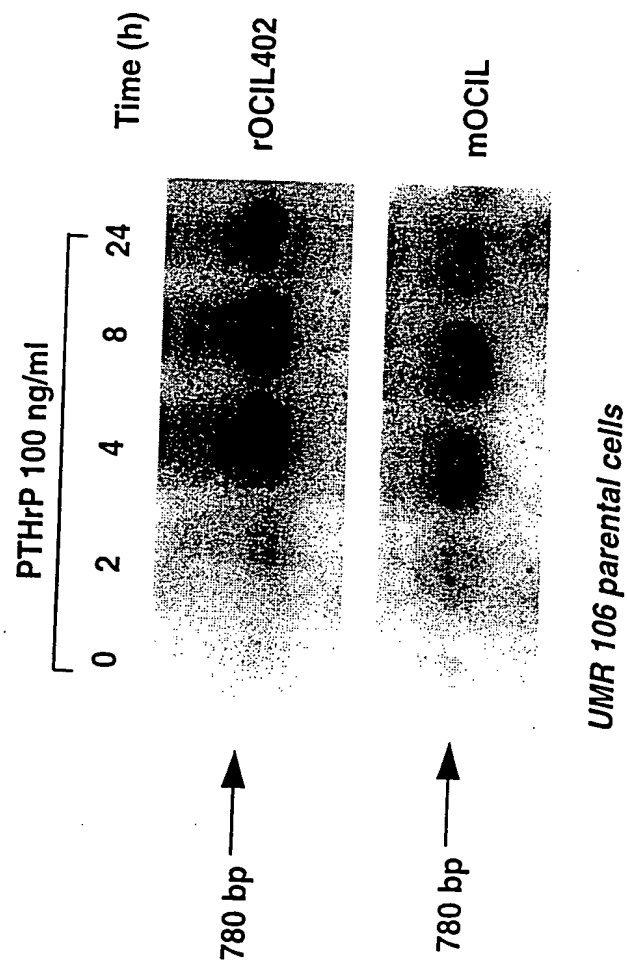
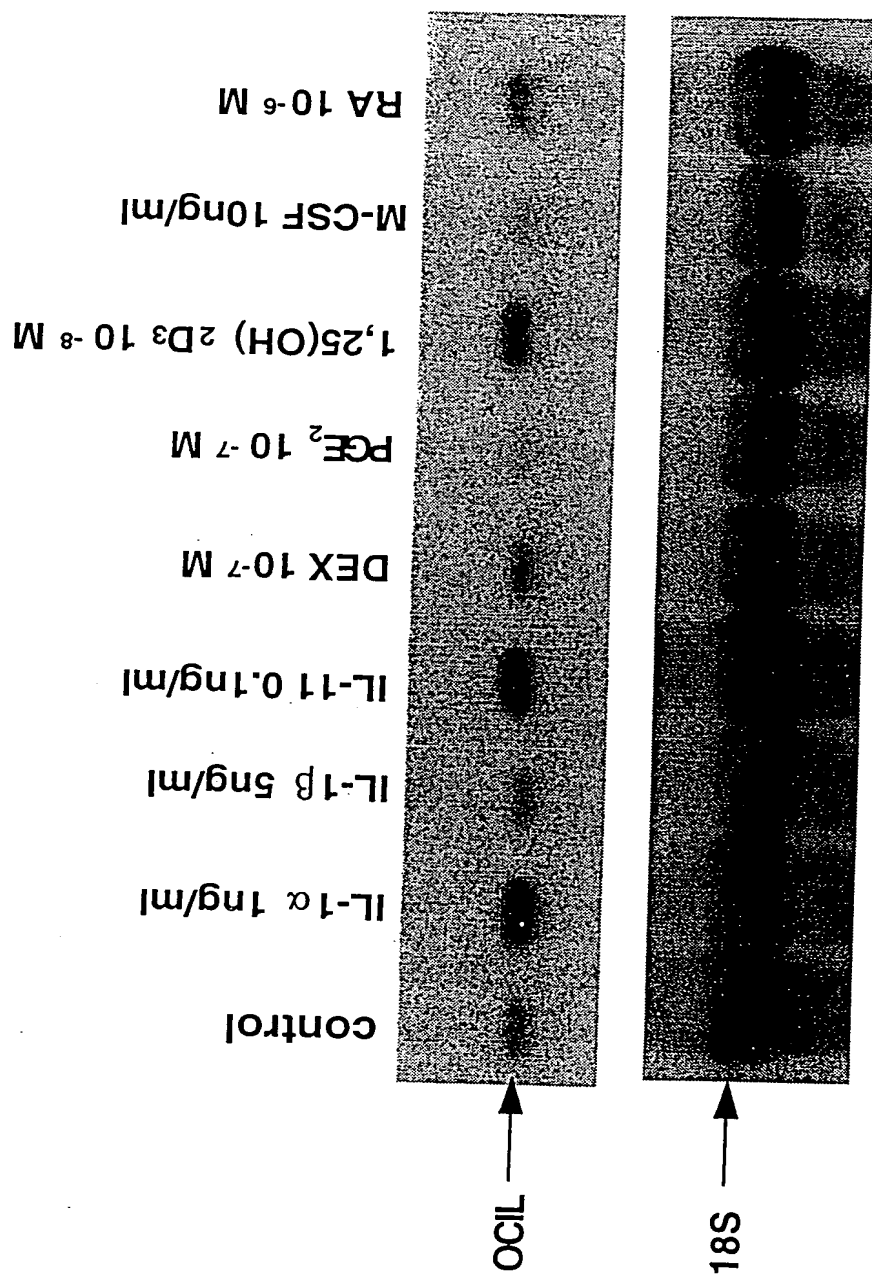


Figure 11B



*Primary calvarial osteoblasts (POB)
24 hours treatment*

FIGURE 12

1,25(OH) $_2$ D $_3$ + PGE $_2$ + DEX

1,25(OH) $_2$ D $_3$ + PGE $_2$

1,25(OH) $_2$ D $_3$ 10 $^{-8}$ M

IL-11 0.1ng/ml

DEX 10 $^{-7}$ M

PGE $_2$ 10 $^{-7}$ M

control

OCIL \uparrow

Mouse stromal cells (ST2)

Figure 13A

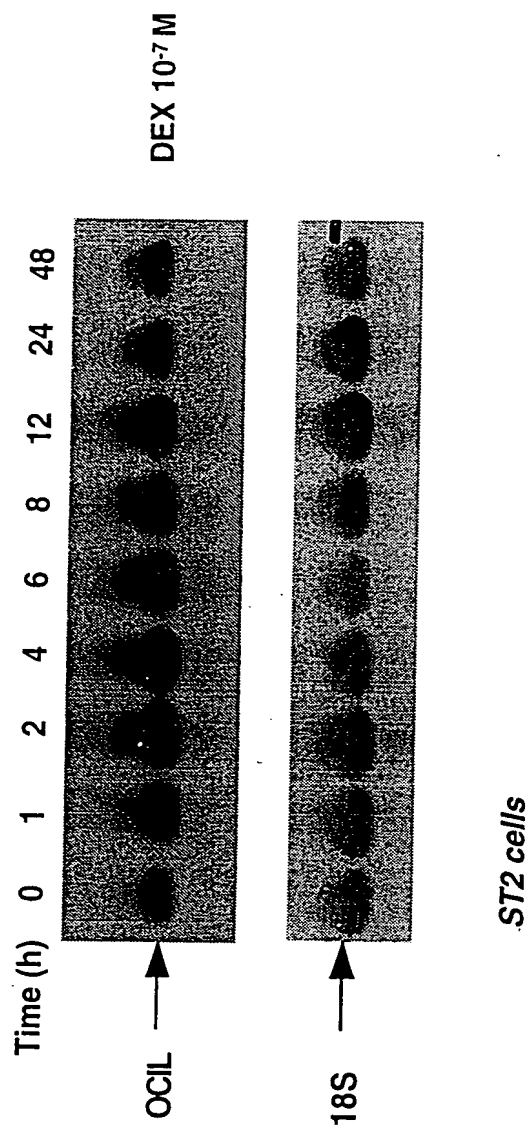


FIGURE 13B

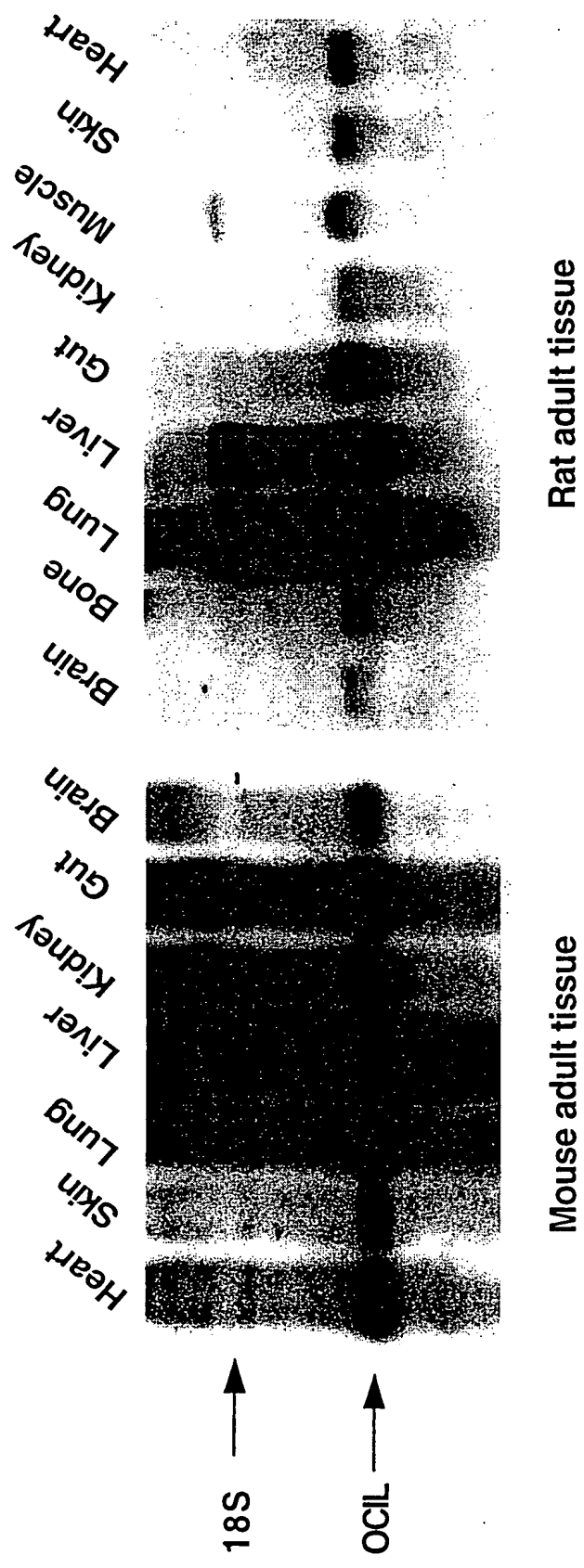
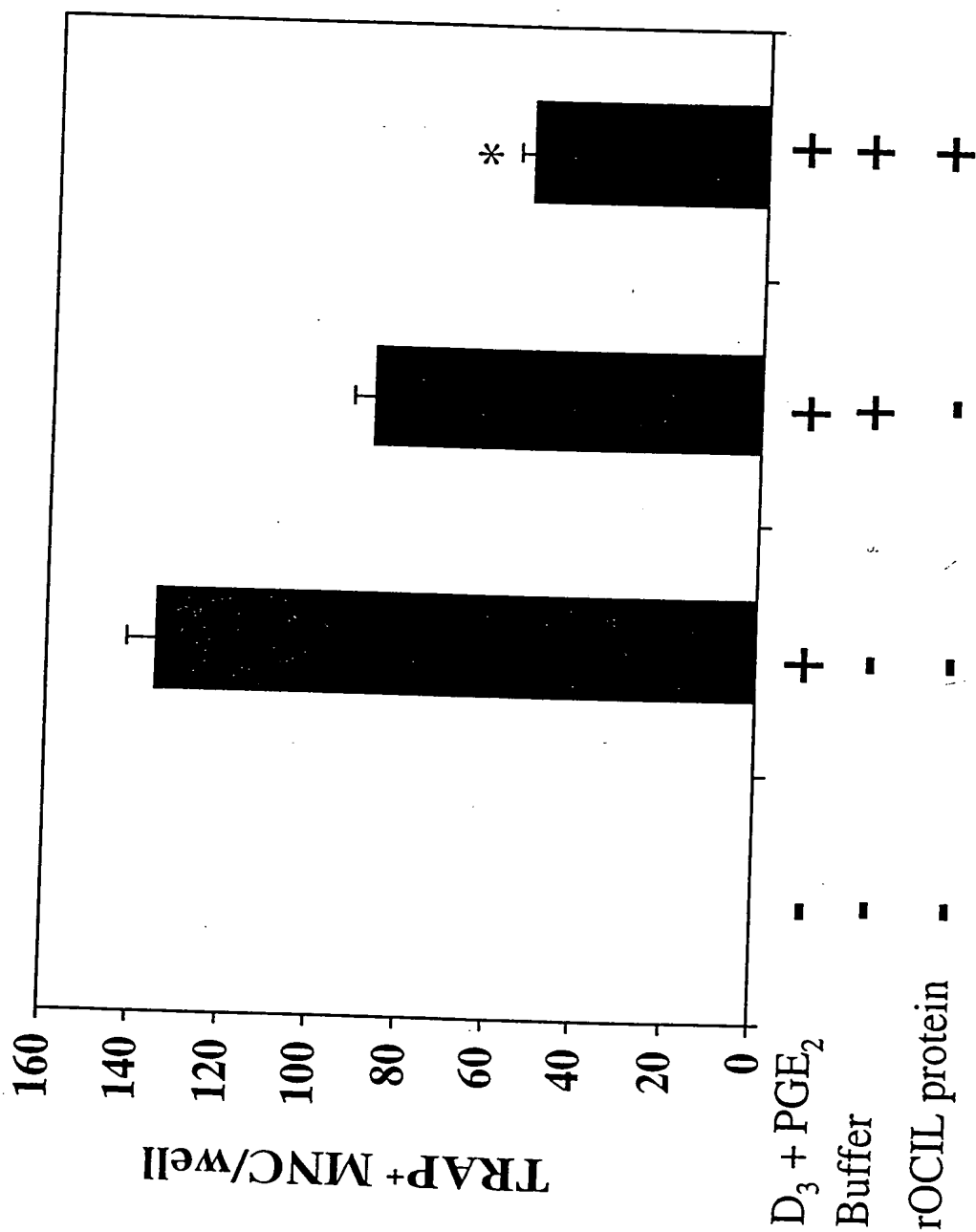


Figure 14

OB + ADULT SPLEEN CO-CULTURE



TRAP: tartrate-resistant acid phosphatase

MNC: multinucleate osteoclasts

*p < 0.025 vs D₃ + PGE₂ treated with buffer alone

Figure 15